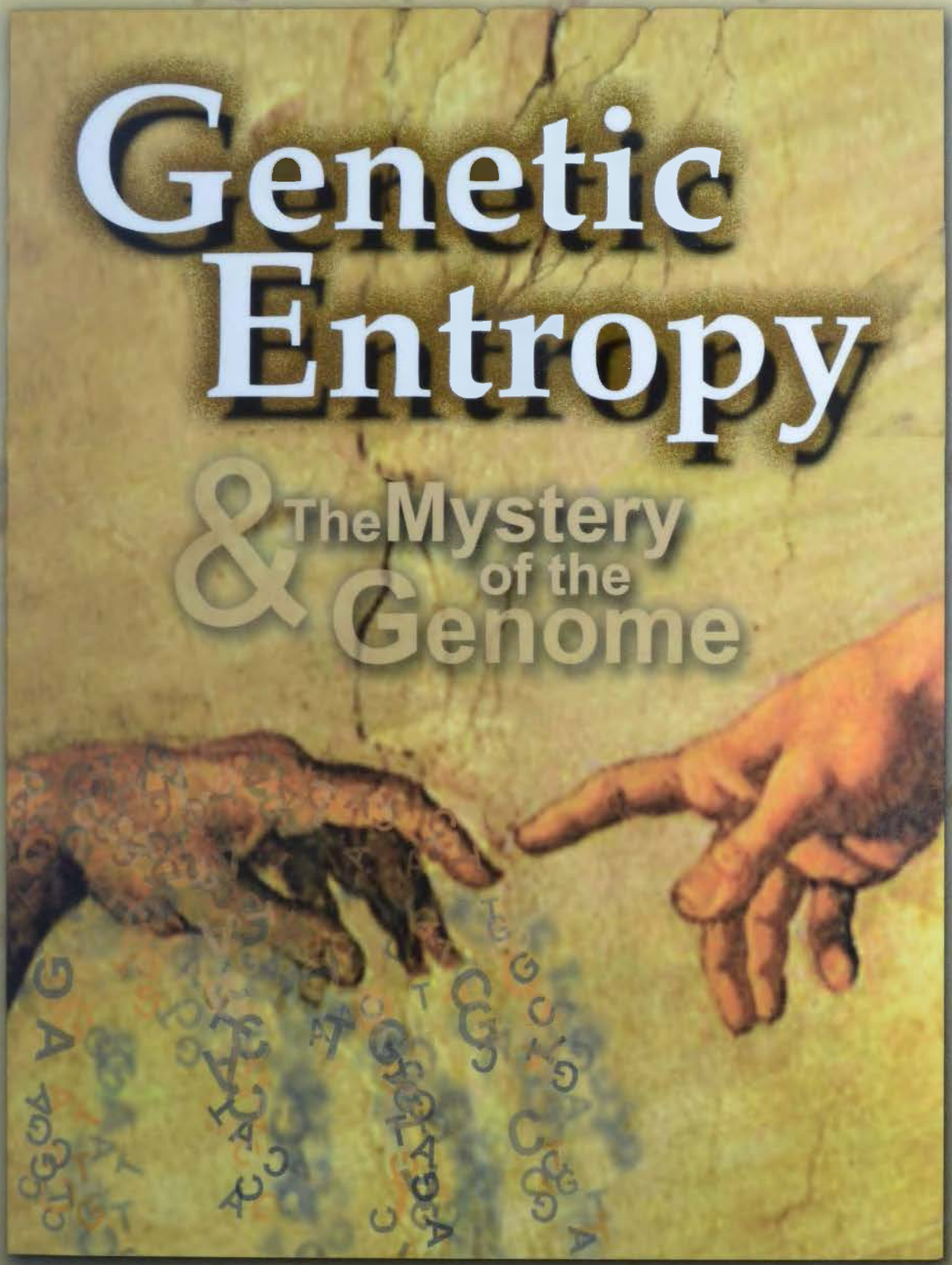
# Genetic Entropy

## & The Mystery of the Genome



Dr. J.C. Sanford

John Sanford

"In *Genetic Entropy*, Cornell University researcher John Sanford lifts the rug to see what evolutionary theory has swept under it. He shows that, not only does Darwinism not have answers for how information got into the genome, it doesn't even have answers for how it could remain there."

*Dr. Michael Behe, Biochemist; Professor of Biological Sciences, Lehigh University; well known author of "Darwin's Black Box".*

"Genetic Entropy is a brilliant expose of the un-reality of the Primary Axiom. It is written in a challenging style, yet is accessible to non-specialists having some minimal background in biology. At the same time, it has sufficient substance and documentation to cause the most highly trained biologist to rethink, in a serious way, what he or she has always believed about the Primary Axiom. In my opinion, this book deserves to be read by every professional biologist and biology teacher in the world. To me it has the potential of changing the outlook of the academic world in a profound way."

*Dr. John Baumgardner is an expert in complex numerical simulations, and has worked for 20 years in the Theoretical Division of the Los Alamos National Laboratory. He has a PhD in geophysics from UCLA and an MS degree in electrical engineering from Princeton.*

"Dr. Sanford is a highly qualified geneticist from a major university. He has written a tremendous book detailing compelling new genetic evidence that the human genome is deteriorating, and that it has always been deteriorating–ever since its origin. The profound implications of these findings should be obvious to any thoughtful person. I believe this easy-to-read and wonderfully convincing little volume should be a must-read for concerned people everywhere."

*Dr. Henry Morris, Late President Emeritus, ICR. Well known author of "The Long War Against God", and approximately 70 other books.*

"I strongly recommend John Sanford's *Genetic Entropy*, which provides a lucid and bold account of how the human genome is deteriorating due to the accumulation of mutations.This situation has disturbing implications for mankind's future, as well as surprising implications concerning mankind's past."

*Professor Phillip Johnson, Emeritus Law Professor, UC-Berkeley; Law Clerk of Chief Justice Earl Warren of the US Supreme Court; author of "Darwin on Trial' and "Reason in the Balance".*

ISBN 978-0-9816316-0-8
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&

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Third Edition

ISBN 978-0-9816316-0-8


**Published by**
FMS Publications
A Division of FMS Foundation
Waterloo, New York

# About the Author

Dr. John Sanford, a Cornell University Professor for more than 25 years, has been semi-retired since 1998. He received his PhD from the University of Wisconsin in the area of plant breeding and plant genetics. While a professor at Cornell, John has trained graduate students and conducted genetic research at the New York State Agricultural Experiment Station in Geneva, NY. During this time, John bred new crop varieties using conventional breeding and then became heavily involved in the newly-emerging field of plant genetic engineering. John has published over 80 scientific publications and has been granted over 30 patents. His most significant scientific contributions involve three inventions, the biolistic ("gene gun") process, pathogen-derived resistance, and genetic immunization. A large fraction of the transgenic crops (in terms of numbers and acreage) grown in the world today were genetically engineered using the gene gun technology developed by John and his collaborators. John also started two biotech enterprises derived from his research, Biolistics, Inc., and Sanford Scientific, Inc. John still holds a position at Cornell (Courtesy Associate Professor), but has largely retired from Cornell and has started a small non-profit organization, Feed My Sheep Foundation.

# Dedication and Acknowledgements

I feel I could only write this little book by God's grace, and acknowledge and thank Him as the giver of every good thing. This book is dedicated to the memory of Dr. Bob Hanneman, my professor and graduate thesis advisor, who encouraged me in my science and provided an example for me regarding faith and godliness. I would like to thank my wife, Helen, for her unswerving support, and my friend, Fred Meiners, for his encouragement. Special thanks to Walter ReMine for his computer simulation of mutation accumulation and Lloyd R. Hight for his artwork. I acknowledge Michael Behe and many others who went before me in recognizing that the Primary Axiom is not true. I am not the last, though I may be the least, to recognize this.

# Genetic Entropy
## & The Mystery of the Genome

# Foreword

By Dr. John Baumgardner

During the past half century, the scientific enterprise has opened a door into an almost surrealistic, Lilliputian realm of self-replicating robotic manufacturing plants, with components whirring at tens of thousands of RPM, automated parcel addressing, transport and distribution systems, and complex monitoring and feedback control systems. Of course, this is the realm of cell and molecular biology. It is a realm in which tens of thousands of different kinds of sophisticated nanomachines perform incredible chemical feats inside the living cell. Above and beyond this cellular complexity is the equally complex realm of the organism, with trillions of cells working in astonishing coordination, and above that is the realm of the brain, with its multiplied trillions of neural connections. Confronted with such staggering complexity, the reflective person naturally asks, "How did all this come to exist?" The standard answer given to this question is what the author of this book calls "the Primary Axiom."

*Genetic Entropy and the Mystery of the Genome* represents a probing analysis of the fundamental underpinnings of the Primary Axiom. In particular, it focuses on the genetic software that specifies life's astounding complexity. The author points out that, for higher organisms, and certainly for humans, the extent of these genetic specifications, called the genome, is vast. Not only is the genome huge, it is also exceedingly complex. It is filled with loops and branches, with genes that regulate other genes that regulate still other genes. In many cases, the same string of genetic letters can code for entirely different messages, depending on context. How

such an astonishing information structure has come into existence is clearly an important question. But the author introduces a further question, namely, how can the human genome even be *maintained* against the degrading effects of the billions of new deleterious mutations that enter the human population each generation?

Concerning the Primary Axiom, the author acknowledges that, as a professional geneticist, he discerned no serious problems with its theoretical underpinnings for many years. He confides that during his training in graduate school he accepted this primarily by trust in the authorities, rather than by genuine personal understanding. At that point he felt he had no choice—he thought this abstract and highly mathematical field was beyond his own ability to assess critically. It was not until much later in his professional career that he became aware of how unrealistic and how vulnerable to critical analysis were the crucial assumptions on which the Axiom rests. The author concludes that most professional biologists today are just like he was earlier in his career. Most simply are not aware of the fundamental problems with the Axiom. This is because the Axiom's foundational assumptions are not critiqued in any serious way, either in graduate classes, or in graduate level textbooks, or even in the professional literature.

The conceptual models that population genetics has offered to the rest of the professional biology community, presented in the guise of mathematical elegance, have at their foundations a number of unjustifiable assumptions. The Primary Axiom, it turns out, depends on these assumptions for its support. Most professional biologists are simply not aware of this state of affairs.

The field of population genetics deals largely with complex mathematical models that attempt to describe how mutations are passed from one generation to the next after they arise, and how they affect the survival of individual members of a population in each generation. The reality of these conceptual models depends

critically, of course, upon the realism of the assumptions on which they are built. In this book the author exposes the obvious lack of realism of many of the most crucial assumptions that have been applied for the past 75 years. Most professional biologists, like the author during the earlier part of his professional career, base much of their confidence in the Primary Axiom on claims derived from these conceptual models that have employed observationally unjustifiable assumptions. Most biologists today are unaware that the claims of population genetics to which they were exposed in graduate school can no longer be defended from a scientific standpoint. Most, therefore, can hardly imagine that when realistic assumptions are applied, population genetics actually repudiates the Axiom.

*Genetic Entropy and The Mystery of the Genome* is a brilliant exposé on the un-reality of the Primary Axiom. It is written in a challenging but accessible style, understandable by non-specialists with a modest background in either genetics or biology. At the same time, this book has sufficient substance and documentation to cause the most highly trained biologist to seriously rethink what he or she probably has always believed about the Primary Axiom. In my opinion, this book deserves to be read by every professional biologist and biology teacher in the world. To me it has the potential of changing the outlook of the academic world in a profound way.

*John Baumgardner has a PhD in geophysics from UCLA and worked as a research scientist in the Theoretical Division of Los Alamos National Laboratory for 20 years. He also received an MS degree in electrical engineering from Princeton University, where he first became aware of information theory and later its implications for biological systems. He is an expert in complex numerical simulations.*

# Prologue

In retrospect, I realize I have wasted much of my life arguing about things that don't really matter. It is my sincere hope that this book can actually address something that really does matter. The issues of *who we are*, *where we come from*, and *where we are going* seem to me to be of enormous importance. This is the real subject of this book.

Modern thinking centers around the premise that man is just the product of a pointless natural process (undirected evolution). This widely-taught doctrine, when taken to its logical conclusion, leads us to believe that we are just meaningless bags of molecules, and in the final analysis, nothing matters. If false, this doctrine has been the most insidious and destructive thought system ever devised by man. Yet, if true, it is at best meaningless, like everything else. The whole thought system which prevails within today's intelligentsia is built upon the ideological foundation of undirected and pointless Darwinian evolution.

Modern Darwinism is fundamentally built upon what I will be calling "The Primary Axiom". The Primary Axiom is that man is merely the product of *random mutations* plus *natural selection*. Within our society's academia, the Primary Axiom is universally taught, and almost universally accepted. It is the constantly-mouthed mantra, repeated endlessly on every college campus. It is very difficult to find any professor on any college campus who would even consider (or, should I say, dare) to question the Primary Axiom. It is for this reason that the overwhelming majority of youth

who start out with a belief that there is more to life than mere chemistry will lose that faith while at college. I believe this is also the cause of the widespread self-destructive and self-denigrating behaviors we see throughout our culture.

What if the Primary Axiom were wrong? If the Primary Axiom could be shown to be wrong, it would profoundly affect our culture, and I believe it would profoundly affect millions of individual lives. It could change the very way we think about ourselves.

Late in my career, I did something that would seem unthinkable for a Cornell professor. I began to question the Primary Axiom. I did this with great fear and trepidation. I knew I would be at odds with the most "sacred cow" within modern academia. Among other things, it might even result in my *expulsion* from the academic world. Although I had achieved considerable success and notoriety within my own particular specialty (applied genetics), it would mean stepping out of the safety of my own little niche. I would have to begin exploring some very big things, including aspects of theoretical genetics which I had always accepted by faith alone. I felt compelled to do all this, but I must confess that I fully expected to simply hit a brick wall. To my own amazement, I gradually realized that the seemingly "great and unassailable fortress" which has been built up around the Primary Axiom is really a house of cards. The Primary Axiom is actually an extremely vulnerable theory. In fact, it is essentially indefensible. Its apparent invincibility derives largely from bluster, smoke, and mirrors. A large part of what keeps the Axiom standing is an almost mystical faith that the "true-believers" have in the omnipotence of natural selection. Furthermore, I began to see that this deep-seated faith

in natural selection is typically coupled with a degree of ideological commitment which can only be described as religious. I started to realize (again with trepidation) that I might be offending the religion of a great number of people!

To question the Primary Axiom required me to re-examine virtually everything I thought I knew about genetics. This was the most difficult intellectual endeavor of my life. Deeply entrenched thought patterns only change very slowly (and, I must add, painfully). What I eventually experienced was a complete overthrow of my previous understanding. Several years of personal struggle resulted in a new and very strong conviction that the Primary Axiom was most definitely wrong. More importantly, I became convinced that the Axiom could be *shown* to be wrong to any reasonable and open-minded individual. This realization was both exhilarating and frightening. I realized that I had a moral obligation to openly challenge this most sacred of cows, but I also realized I would earn for myself the intense disdain of most of my colleagues within academia, not to mention very intense opposition and anger from other high places.

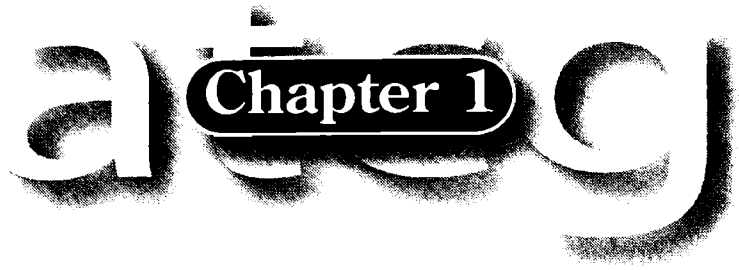
What should I do? It has become my conviction that the Primary Axiom is insidious on the highest level, having a catastrophic impact on countless human lives. Furthermore, every form of objective analysis I have performed has convinced me that the Axiom is clearly false. So now, regardless of the consequences, I have to say it out loud: ***the Emperor has no clothes!***

I invite the reader to carefully consider this very important issue. Are you really just a meaningless bag of molecules, the product of

nothing more than random molecular mutations and reproductive filtering? As you read this book, I am going to ask you to wrap your mind around something very challenging but also very exciting. I contend that, if you will invest a reasonable mental effort and follow just a handful of fairly simple arguments, I can persuade you that the Primary Axiom is false. Can you imagine anything more radical or more liberating? To the extent that the Primary Axiom can be shown to be false, it should have a major impact on your own life and on the world at large. For this reason, I have dared to write this humble little book, which some will receive as blasphemous treason and others as revelation.

If the Primary Axiom is wrong, there is a surprising and very practical consequence. When subjected only to natural forces, the human genome must irrevocably degenerate over time. Such a sober realization should have more than just intellectual or historical significance. It should rightfully cause us to personally reconsider where we should rationally be placing our hope for the future.

*Author's note: Since the initial writing of this book, a series of dramatic new developments have been published, all of which powerfully reinforce the central themes of this book. These developments include the demonstration of the nonlinear nature of the genome, the poly-functional nature of each nucleotide, the fact that the genome encodes much more information than was even recently thought possible, and the nonexistence of "junk" or "silent" DNA. I have added very brief "Author's notes" on these various points, for the reader's interest.*




# The Genome is the Book of Life. Where Did it Come From?

*Newsflash – The genome is an instruction manual.*

An organism's **genome** is the sum total of all its genetic parts, including all its chromosomes, genes, and nucleotides. A genome is an instruction manual that specifies a particular form of life. The human genome is a manual that instructs human cells to be human cells and the human body to be the human body. There is no information system designed by man that can even begin to compare to the simplest genome in complexity.

The complex nature of the genome can only be appreciated when we begin to grasp how much information it contains. When you assemble the little red wagon you bought for your child on Christmas Eve, there is a booklet that tells you how to put it together. The size of the booklet is deceptive. It does not contain all the information needed for fabricating the component parts, or for manufacturing the steel, rubber, and paint. The complete instruction manual would actually be a very substantial volume. If you compiled all the instruction manuals associated with creating a modern automobile, it would fill a small library. That library would be very large if it included the information needed for making the components and for assembling the robotic assembly lines. Likewise, the manuals required for creating a jet fighter and

all its components, computers, and assembly lines would comprise an extremely large library. The manuals needed for building the entire space shuttle and all its components and all its support systems would be truly enormous! Yet the *specified complexity* of even the simplest form of life is arguably as great as that of the space shuttle. Try to absorb the fact that the jump in complexity from a bacterium to a human being is arguably as great as the jump from the little red wagon to the space shuttle! There is simply no human technology that serves as an adequate analogy for the complexity of a human life. The genome is the instruction manual encoding all the information needed for that life!

We have thus far only discovered the first dimension of this book of life: a linear sequence of four types of extremely small molecules, called nucleotides. These small molecules make up the individual steps of the spiral-staircase structure of DNA. These molecules are the letters of the genetic code, and are shown symbolically as A, T, C, and G. These letters are strung together like a linear text. They are not just symbolically shown as letters, they are very literally the *letters* of our instruction manual. Small clusters or motifs of these four molecular letters make up the *words* of our manual, which combine to form genes (the *chapters* of our manual), which combine to form chromosomes (the *volumes* of our manual), which combine to form the whole genome (the entire *library*).

A complete human genome consists of two sets of 3 billion individual letters each. Only a very small fraction of this genetic library is required to directly encode the roughly 100,000 different human proteins and the uncounted number of functional RNA molecules found within our cells. Each of these protein and RNA molecules are essentially miniature *machines*, each with hundreds

of component parts, and with its own exquisite complexity, design, and function. But the genome's *linear* information, equivalent to many complete sets of a large encyclopedia, is not enough to explain the complexity of life.

As marvelous as all this linear information is, it must only be the first dimension of complexity within the genome. The genome is not just a simple string of letters spelling out a linear series of instructions. It actually embodies multiple linear codes that overlap and constitute an exceedingly sophisticated information system embodying what is called *data compression* (Chapter 9).

In addition to multiple, overlapping, linear, language-like forms of genetic information, the genome is full of countless loops and branches, like a computer program. It has genes that regulate genes that regulate genes. It has genes that sense changes in the environment and then instruct other genes to react by setting in motion complex cascades of events that can then respond to the environmental cue. Some genes actively rearrange themselves, or modify and methylate other gene sequences, basically *changing* portions of the instruction manual!

Lastly, there is good evidence that linear DNA can fold into two- and three-dimensional structures (as do proteins and RNAs), and that such folding probably encodes still higher levels of information. Within the typical non-dividing nucleus, there is reason to believe there may be fabulously complex three-dimensional arrays of DNA, whose 3-D architecture controls higher biological functions.

The bottom line is this: the genome's set of instructions is not a simple, static, linear array of letters, but is dynamic, self-regulating, and multi-dimensional. There is no human information system

that can even begin to compare to it. The genome's highest levels of complexity and interaction are probably beyond the reach of our understanding, yet we can at least acknowledge that this higher level of information must exist. So while the linear information within the human genome is limited, the non-linear information must obviously be much, much greater. Given the unsurpassed complexity of life, this necessarily has to be true.

All this information is contained within a genomic package that is, in turn, contained within a cell's nucleus–a space much smaller than a speck of dust. Each human body contains a galaxy of cells–more than 100 trillion–and every one of these cells has a complete set of instructions and its own highly-prescribed duties. The human genome not only specifies the complexity of our cells and our bodies, but also the functioning of our brains. The structure and organization of our brains involves a level of organization entirely beyond our comprehension.

As we recognize the higher-order dimensions of the genome, I believe we can readily agree with Carl Sagan's oft-repeated statement that each cell contains more information than the Library of Congress. Indeed, human life is more complex than all human technologies combined! **Where did all this information come from, and how can it possibly be maintained? This is the mystery of the genome.**

The standard answer to the origin of biological information is that *mutation* and *selection* have created all biological information. This is the fundamental basis of *Neo-Darwinian Theory*. It says that all genomes (instruction manuals) must have derived from a

simple initial genome via a long series of mutations (typographical errors) and lots of natural selection (differential copying). This is the *Primary Axiom* of biological evolution: **Life is life because random mutations at the molecular level are filtered through a reproductive sieve acting on the level of the whole organism.** What is an axiom? An axiom is a concept that is not testable and is accepted by faith because it seems obviously true to all reasonable parties. On this basis, it is accepted as an Absolute Truth. In this book, I am going to urge the reader to ask the question, "Should we accept today's Primary Axiom?" If the Primary Axiom could be shown to be wrong, it would mean that our current understanding of the history of life is also wrong. This would justify a *paradigm shift* of the highest magnitude (a paradigm shift is a change in a fundamental idea that once governed a group's collective thinking), and would allow us to completely reevaluate many of the deeply entrenched concepts which frame modern thinking.

It is important that we put the Primary Axiom into a framework that is honest and also realistic to our mind's eye. I would like to propose an honest analogy which very accurately characterizes today's Primary Axiom. My analogy involves the evolution of transportation technologies, as outlined below.

In our little red wagon analogy, the first primeval genome encoded the assembly instructions for the first wagon. That simple genomic instruction manual was copied by an invisible mechanical scribe, to make more instruction manuals. Each newly copied manual was used to make a new red wagon. However, the scribe, being imperfect, made errors. So each wagon came out differently. Each

wagon had its own unique instruction manual taped to its bottom. When the first wagons were junked, their instruction manuals were also junked. New copies of instruction manuals could only be imperfectly copied from the manuals of the immediately preceding generation of wagons, just before they were to be discarded. Since the copying of instructions was sequential (rather than using an original master copy), errors accumulated over time in every manual, and the resulting wagons started to change and vary. The accumulating errors are, of course, our analogy for mutations.

Are you uneasy with this picture? No doubt you realize we are looking at a deteriorating situation. Information is being lost, instructions are becoming degraded, and the wagons will doubtless deteriorate in quality. Eventually, the system will break down, the manual will become complete gibberish, and workable wagons will become extinct. We will examine this problematic aspect of mutation in more detail in Chapters 2 and 3.

At this point, we introduce our hero, natural selection. Natural selection is like a judge, or quality control agent, deciding which wagons are suitable models for further copying. Natural selection, as the judge, instructs the scribe not to copy manuals from inferior wagons. This represents differential reproduction (reproductive sieving), better known as *selection*. But it is important to understand there is never direct selection for good instructions, only for good wagons. As we will see, this is very important. Mutations are complex and happen at the molecular level, but selection can only be carried out on the level of the whole organism. The scribe and judge work entirely independently. The scribe is essentially blind, working on the level of molecules, and, being extremely near-

sighted, he can only see individual letters while he is copying. The judge is also nearly blind, but he is extremely far-sighted. He never sees the letters of the manual, or even the wagon's individual components. He can only see the relative performance of the whole wagon.

The scribe can be envisioned at the beginning of a robotic assembly line. He copies programs for the robots by blindly and imperfectly duplicating older programs, one binary bit at a time. The quality control agent looks at the performance of the finished wagons, and decides which wagons are better than others. The programs from the wagons he has chosen are then given to the scribe for the next round of copying and assembly.

In this way, many defective wagons can be eliminated, and so most errors in the instructions might presumably be eliminated. More exciting, some rare spelling errors might result in *better* wagons, and so the judge can instruct the scribe to preferentially copy these instructions. The process of evolution has begun!

Let us now examine the feasibility of the selection process as a mechanism for improving genomic information. The information within the instruction manual might not only be *improved* by this process, but it can also be *expanded.* If the imperfect scribe occasionally copies an extra (duplicate) page out of the manual, we might start adding information. Naturally, a duplicate page in an instruction manual is not really new information. In fact, it will invariably confuse and disrupt the reading of the manual. But again, the judge only allows copying of manuals from *good wagons.* So, bad duplications might presumably be eliminated and

harmless duplications might be preserved. Now these harmless duplications will also begin to have copying errors within them, and some of these errors *might* create new and useful information, like instructions for new functional components in the wagon. With a little imagination, perhaps we can picture a variety of duplications eventually evolving, via misspellings, and specifying something entirely new, like an internal combustion engine, or wings, or an on-board computer navigational system. Hence we have a scenario whereby a little red wagon can, through a series of typographical errors, evolve into an automobile, a plane, or even the Space Shuttle.

But this analogy does not go far enough, because a human being is much more complex than a space shuttle. In fact, our **phenome** (the entire body including the brain), is immeasurably more complex than any known technology. Perhaps we can come closer to the mark if we imagine our little red wagon being transformed into the fanciful *Starship Phenome*, complete with warp-speed engines and a holodeck (Figure 1a-d, pp. 11-13). The Primary Axiom says that misspellings and some differential copying can simultaneously explain the library (the genome) and the starship (the phenome) illustrated in Figure 1d.

We must now ask, "Could misspellings and selective copying really do this?" A correct understanding of *selection* is essential for evaluating the merit of the Primary Axiom. No intelligence is involved in this scenario. The scribe is really just a complex array of senseless molecular machines that blindly replicate DNA. The judge is just the tendency for some individuals to reproduce more than others. Many people unconsciously attribute to natural selection a type of supernatural intelligence. But natural selection

is just a term for a blind and purposeless process whereby some things reproduce more than others. It is crucial we understand that our scribe and our judge have neither foresight nor intelligence. Their combined IQ equals *zero*.

**Isn't it remarkable that the Primary Axiom of biological evolution essentially claims that typographical errors and minimal selective copying can transform a wagon into a spaceship in the absence of any intelligence, purpose, or design? Do you find this concept credible?** It becomes even more startling when we realize that the spaceship was in no way pre-specified under the Primary Axiom, not even in the mind of God. It truly "just happened" by accident. The spaceship is essentially just a *mutant wagon*. Yet this illustration is actually the best analogy for describing the Primary Axiom. The only weakness of this analogy is that there is no human technology that can compare to the actual complexity of life, and thus there is no human information system that can compare to the human genome.

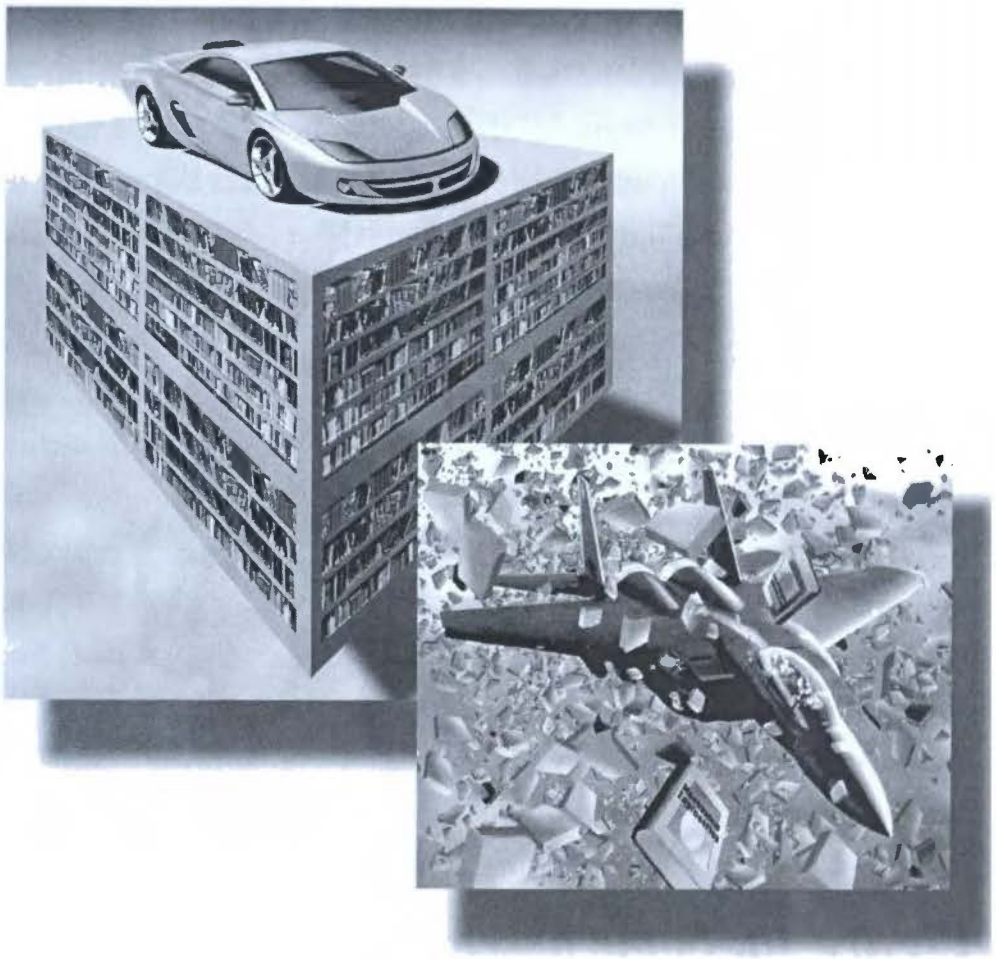
This whole analogy stands in sharp contrast to the false picture portrayed by Dawkins (1986). The famous Dawkins argument, built around the phrase "me thinks it is like a weasel", involved a *pre-specified message* being systematically uncovered through a simple-minded process equivalent to the children's games "20 Questions" or "Hangman". In Dawkins' model, both the phrase and the carefully crafted and finely tuned method of uncovering it were intelligently designed and purposeful. Furthermore, his selection scheme allowed for direct selection of genotype (misspellings) rather than phenotype (wagon performance). Briefly, Dawkins set up a simple computer program which started with a simple random

array of letters, having exactly the same number of characters as the phrase "me thinks it is like a weasel". He designed his program to then begin to randomly mutate (change) the letters. When a new letter fell into place which matched the phrase "me thinks it is like a weasel" the program would select the "improved" message. Obviously it would not take long for such a little program to create the desired phrase. However, even to make this simple program work, Dawkins had to carefully design the replication rate, the mutation rate, and other parameters to get the results he wanted. This program supposedly proved that evolution via mutation/selection is inevitable (not requiring any intelligent design). Obviously, Dawkins used an intelligently designed computer, and then he used his own intelligence to design the program, to optimize it, and even to design the pre-selected phrase. For many reasons, Dawkins' argument cannot honestly be used to defend the Primary Axiom (which does not allow for the operation of any intelligence, purpose, or forethought, and does not allow for direct selection for misspellings themselves).

In this book we are going to examine some basic aspects of genetics and determine if the known facts about the human genome are compatible with the Primary Axiom. As you read, if you come to the point where you feel that the Primary Axiom is no longer obviously true to all reasonable parties, then you should feel rationally obligated to reject it as an *axiom*. If the Primary Axiom cannot stand up as an axiom, it should be treated as an unproven hypothesis, subject to falsification.


## *Figure 1a: Some assembly required...*

A little red wagon is not information, but it requires information to specify its assembly. A typical assembly booklet is not really all the information required to specify the production of a wagon. The truly complete production manual would be a very substantial book, specifying the production of all the components (wheels, etc.), and all raw materials (steel, paint, rubber).



## *Figure 1b.*

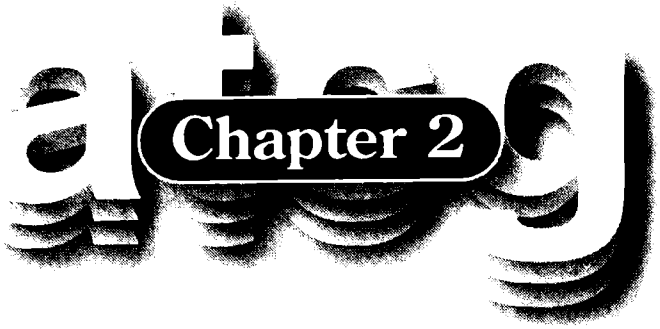
The complete instructions needed to specify a modern automobile would comprise a substantial library. If the assembly was to be done entirely by machines (no "intelligence" required), the information, including that required for making and programming the robots, would be massive, comprising a phenomenal collection of books.

## *Figure 1c.*

The complete instruction manual needed to specify a jet fighter, including its on-board computer systems and all the manufacturing and support systems inherent in creating and maintaining such a system, would be a massive library. Imagine the instructions if every component had to be made robotically!


## *Figure 1d.*

The library shown above represents the human genome (all our genetic information). The spaceship represents the human phenome (our entire body, including our brain). We cannot really imagine how extensive the library would have to be were it to specify the fictional S.S. Phenome, complete with warp-speed engines and a holodeck. Wouldn't it have to be much larger than the Library of Congress? Yet it can be reasonably argued that a human is still more complex than a hypothetical S.S. Phenome. What type of starship could reproduce itself?




# Are Random Mutations Good?

*Newsflash – Random mutations consistently destroy information.*

The subject of mutation in the human genome should be approached with sensitivity because people matter and people are hurt by mutation. The number of families affected by birth defects is tragically high, so this is not just a matter of "statistics". Genetic disease, in its broadest sense, is catastrophic. If we include all genetic predispositions to all pathologies, we must conclude that we are *all* highly mutant. Furthermore, nearly every family is impacted by the tragedy of cancer, which is fundamentally the result of mutations within our body cells. Indeed, growing evidence indicates that *aging* itself is due to the accumulation of mutations within the cells of our body. Mutations are the source of immeasurable heartache. In fact, they are inexorably killing each one of us. So mutations are more than just an academic concern!

Can we say mutations are good? Nearly all health policies are aimed at reducing or minimizing mutation. Most personal health regimes are aimed at reducing mutations, to reduce risk of cancer and other degenerative diseases. How can anyone see mutation as good? Yet, according to the Primary Axiom, mutations are good because they create the variation and diversity which allow selection and evolution to occur, thus creating the information needed for life.

Before we go further, we need to realize that there are two types of variation: random variation and designed variation. Random variation is the type of variation I see in my car as time passes. It is the rust, the dings, the scratches, and broken parts. Such things create variation in cars, but do they ever lead to better cars? Can typographical errors realistically improve a student's term paper? Can throwing rocks improve a glass house? Apart from accidents, there exists another type of variation, designed variation. When I bought my car I had many options: paint color, type of tire, size of engine, etc. These options were useful to me in making my selection. These designed variable components have also proven useful to me later on. I have added or taken away various options, replaced broken parts, etc. These designed forms of variation are beneficial, being useful for sustaining my car, and are even useful for *improving* my car, within limits. However, such variations, even when they are intelligently designed, will never transform my car into a spaceship.

Part of the Primary Axiom is that all genetic variation *must* come from random mutations, since no genetic variation by design is allowed. However, now that the era of genetic engineering has begun, this axiomatic assumption clearly is not true (because many living organisms now contain genetic variations designed and engineered by man). Perhaps this simple fact can open our minds to the possibility of designed genetic variation which preceded man! Apart from our ideological commitment to the Primary Axiom, it can very reasonably be argued that random mutations are never good. Speaking in terms of vehicles, they appear to be the *dings* and *scratches* of life, rather than the spare parts.

The overwhelmingly deleterious nature of mutations can be seen by the incredible scarcity of clear cases of information-creating mutations. It must be understood that scientists have a very sensitive and extensive network for detecting information-creating mutations, and most geneticists are diligently keeping their eyes open for them all the time. This has been true for about 100 years. The sensitivity of this observational network is such that even if only one mutation out of a million unambiguously creates new information (apart from fine-tuning), the literature would be overflowing with reports of this happening. Yet I am still not convinced there is a single, crystal-clear example of a known mutation which unambiguously *created* information. There are certainly many mutations which have been described as beneficial, but most of these beneficial mutations have not created information, but rather have destroyed it. For illustration, some of us (like me) would view a broken car alarm as "beneficial". However, such random changes, although they might be found to be "desirable", still represent a breakdown and not the creation of a new functional feature. Information decreases. This is the actual case, for example, in chromosomal mutations that lead to antibiotic resistance in bacteria, cell functions are routinely lost. The resistant bacterium has not evolved. In fact it has digressed genetically and is *defective*. Such a mutant strain is rapidly replaced by the superior, natural bacteria as soon as the antibiotic is removed. Another example would be the hairless Chihuahua dog. In extreme heat, reduction of size and loss of hair may be useful adaptation, but this involves degeneration, not creation of new information. In such situations, although local adaptation is occurring, information is being lost, not added. Yet the Primary Axiom still insists mutations are good and are the building blocks with which evolution creates the

galaxy of information currently existing within the genome. Let us continue to examine this concept more closely.

The nature of genetic deterioration via mutation can easily be seen using our analogy of an instruction manual. For example, a single line within a jet aircraft assembly manual might read as follows:

> *Step 6. When you have completed the last step, go back and repeat step 3, until part B is 10.004 mm thick. Then wait, no less than 3h, before going to the next step.*

Limiting ourselves to just simple point mutations (misspellings), there are three possible levels of impact on the above instructions. Theoretically, some misspellings might have zero impact on the message (I don't see any obvious examples in this instance). Most misspellings will have a very subtle effect on the clarity or coherence of the message (i.e., misspellings within all the portions not underlined). Lastly, a few changes (within the underlined areas), will have the potential for dramatic (essentially lethal) effects. What is *not* clear in the above example is which misspellings could actually improve the instructions to result in a better jet plane. While such changes are *conceivable*, they are unlikely, on a level that is difficult to fully describe. Any *possible* improvement in the instructions deriving from a misspelling would be expected to be very slight (i.e., changing the 4 to an 8, three places to the right of the decimal in the specified thickness). These types of changes do not actually *add* information, but really only *modulate,* or fine-tune, the system. It should be obvious to any reasonable person that we can't expect *any* misspellings that would result in a major advance in jet technology. For example, no misspelling in

the above sentence is going to create a new patentable component. Such major changes would obviously require intelligent design. For every hypothetical misspelling that might very subtly improve (or, more accurately, modulate) a jet plane's blueprint. there would be a multitude of misspellings which would be detrimental. The detrimental changes would range from a few lethal errors to a very large number of nearly-neutral changes in the text.

The above illustration can be extended to the genome (see Figure 2, p. 28). There are over 3 billion potential point mutation sites in the human genome. Only a small fraction of these, when mutated, will have a major effect. Yet none of the potential mutations can be conclusively shown to have zero effect. The vast bulk of the nucleotide positions are considered to be "nearly-neutral" sites, as will be seen more clearly below. Misspellings in life's instruction manual will sometimes be very deleterious, but in the overwhelming majority of cases they will be only very slightly deleterious. No new information can be expected, although existing information can be modulated or fine-tuned to a limited extent. Biological modulation would involve adjusting the cell's "rheostats". For example, it is well known that mutations can adjust activity of a promoter or enzyme, either up or down. However, when we use a rheostat to dim a light, we are not creating a new circuit, nor are we in any way creating new information. We are just fine-tuning the system that is already there, which was, in fact, *designed to be fine-tuned.*

I have just stated that the overwhelming majority of mutations should be nearly neutral. All population geneticists would agree, for many reasons. First, it can be seen by the nature of misspellings in any written language (as you can picture for yourself by changing

any single letter in this book). Second, it can be seen by the total number of nucleotides. On average, each nucleotide position can only contain one 3-billionth of the total information. Third, it can be seen from innumerable studies on the mutation of specific coding sequences, promoters and enhancers. Experimentally, we can show that most nucleotide positions have very subtle effects on any given cell function, and only a few mutations are real "killers" of gene function (remember, any single gene function is just a miniscule part of the whole cell's system). Lastly, the near-neutral impact of most nucleotides can be seen from the very subtle role that single nucleotides play in *genome-wide patterns* (codon-preferences, nucleosome binding sites, isochores, "word" compositional differences between species, etc.). These patterns involve hundreds of millions of nucleotides which are dispersed throughout the genome. Individual nucleotide positions must play an immeasurably tiny role in maintaining all such genome-wide patterns. Yet as infinitesimal as these effects are, they are not zero. Such patterns exist because each nucleotide contributes to it. Each nucleotide still has an impact, and so carries information. No matter how we analyze it, we will see that most nucleotide positions must be overwhelmingly nearly neutral.

Are there *truly neutral* nucleotide positions? True neutrality can never actually be demonstrated experimentally (it would require infinite sensitivity). However, for reasons we will get into later, some geneticists have been eager to minimize the functional genome and have wanted to relegate the vast bulk of the genome to "junk DNA". Mutations in such DNA are assumed to be entirely neutral. However, actual research findings continually expand the size of the functional genome, while the presumed junk DNA

keeps shrinking. In just a few years, many geneticists have shifted from believing that less than 3% of the total genome is functional to believing that more than 30% is functional, and that fraction is still growing. As the functional genome expands, the likelihood of neutral mutations shrinks. Moreover, there are strong theoretical reasons for believing that there is no truly neutral nucleotide position. By its very existence, a nucleotide position takes up space, affects spacing between other sites, and affects such things as regional nucleotide composition, DNA folding, and nucleosome binding. If a nucleotide carries *absolutely no* information, it is, by definition, slightly deleterious, as it slows cell replication and wastes energy. Just as there are really no truly neutral letters in an encyclopedia, there are probably no truly neutral nucleotide sites in the genome. Therefore there is no way to change any given site without *some* biological effect, no matter how subtle. While most sites are probably nearly neutral, very few, if any, should be absolutely neutral.

So what does the real distribution of all mutations really look like? Figure 3a (p. 29) shows the naive, bell-shaped curve view of mutation, with half of the mutations being beneficial and half being deleterious. It is easy to envision selective progress with such a distribution of mutations. Selection would obviously favor the good mutations and eliminate the bad. In fact, if this distribution were correct, progressive evolution would be inevitable. But this view is clearly incorrect. **Beneficial mutations are so rare that they are typically not shown in such graphs.** Figure 3b (p. 30) shows a more realistic view of the distribution of mutations, ranging from lethal (-1) to neutral (0). However, this is still not quite right. Mutations are sharply skewed toward neutral values.

In other words, most mutations are nearly neutral, as we have just discussed. What does the real distribution of mutations look like? Figure 3c (p. 31) is modified and expanded from Kimura (1979). This curve very nearly represents the true distribution of mutations.

As can be seen from Kimura's curve, most mutations are negative, and pile up steeply near the zero mark. They are deleterious and overwhelmingly nearly neutral. Kimura is famous for showing that there is a "zone of near-neutrality" (shown here as a box). Kimura calls near-neutral mutations "effectively neutral", meaning that they are so subtle that they are *not subject to selection*. However, we can see that Kimura does not show *any* mutations as being *absolutely* neutral. His curve approaches, but does not reach, the zero-impact point. Kimura's somewhat arbitrary cut-off point for "unselectable" (i.e., the size of his box) he calculates as a function of $N_e$ (the number of reproducing individuals within a breeding population.)

It is important to note that Kimura's box size, which he calculates based upon population size, is only a minimal estimate of the extent of the effectively neutral mutations. The actual box size should also be enlarged by any and all non-genetic factors that can affect reproductive probability. As we will see in Chapter 6, this fact very *significantly increases the size of the box* (see Figure 9, p. 104). *Anything that decreases the "signal-to-noise ratio" will make proportionately more of a genome's nucleotides unselectable.* The importance of non-genetic factors in terms of making proportionately more nucleotides unselectable is acknowledged by the famous geneticist Muller (Muller, 1964).

In Kimura's figure, he does not show any mutations to the right of zero–there are zero beneficial mutations shown. He obviously considered beneficial mutations so rare as to be outside of consideration. Given this distribution of mutations, one would naturally ask, "How can theorists possibly explain evolutionary progress?" It is done as follows: everything in the "near-neutral box" is redefined as being *completely neutral*, and is thereby dismissed. It is then assumed that the mutations to the left of the near-neutral box can be entirely eliminated using natural selection. Having eliminated *all* deleterious mutations in these two ways, the theorists are then free to argue that no matter how rare beneficial mutations may be (to the right of the box), there should now be enough time and enough selection power left over to rescue them and to use them as the building blocks of evolution. As we will soon see, they are wrong on all counts. The mutations in the box cannot be dismissed, the mutations to the left of the box cannot necessarily all be eliminated by selection, and there is neither time nor selection power left for selecting the extremely rare beneficial mutations which might occur to the right of the near-neutral box.

Given the pivotal role beneficial mutations play in all evolutionary scenarios, I was puzzled as to why Kimura did not represent them in any way in his graph. In fairness I thought I should sketch them in. To the extent they occur, the distribution curve for beneficial mutations should be a reverse image of the deleterious mutations. Just like deleterious mutations, the overwhelming majority of the beneficial mutations should be nearly neutral, being crowded toward the neutral mark. Crow (1997) clearly states this obvious fact. The overwhelming majority of beneficial mutations should

have very slight effects (see Appendix 5 for more details). However, since beneficial mutations are so rare compared to deleterious mutations, their range and the area under their curve would also be proportionally smaller. I have seen estimates of the ratio of deleterious-to-beneficial mutations ranging from one thousand to one up to one million to one. The best estimates seem to be one million to one (Gerrish and Lenski, 1998). The actual rate of beneficial mutations is so extremely low as to thwart any actual measurement (Bataillon, 2000; Elena et al., 1998). Therefore, I cannot draw a small enough curve to the right of zero to accurately represent how rare such beneficial mutations really are. Instead, I have just placed an easily visible triangle there (Figure 3d, p. 32). Figure 3d is an honest and true representation of the natural distribution of mutations, except that it is vastly too generous in terms of beneficial mutations. What is most interesting about this figure (and it came as a shock to me) is the realization that essentially the entire range of all hypothetical beneficial mutations falls within Kimura's "effectively neutral" zone. That means that essentially all beneficial mutations (to the extent they actually happen), must be "unselectable". So selection could never favor any such beneficial mutations, and they would essentially all drift out of the population. No wonder Kimura preferred not to represent the distribution of the favorable mutations!

Figure 3d vividly illustrates why mutations cannot result in a net gain of information. As we will see more clearly in later chapters, selection cannot touch any of the mutations in the near-neutral box. Therefore, the very strong predominance of deleterious mutations in this box absolutely guarantees net loss of information. Furthermore, when mutation rate is high and reproductive rate is

moderate or low, selection cannot even eliminate all the deleterious mutations to the *left* of the box. We will see that constraints on selection even limit our ability to select for the extremely rare beneficial mutation that might lie to the right of the near-neutral box. **Everything about the true distribution of mutations argues against their possible role in forward evolution.**

Because beneficial mutations are so central to the viability of the Primary Axiom, I need to say a little more about them. During the last century, there was a great deal of effort invested in trying to use mutation to generate useful variation. This was especially true in my own area, plant breeding. When it was discovered that certain forms of radiation and certain chemicals were powerful mutagenic agents, millions and million of plants were mutagenized and screened for possible improvements. Assuming the Primary Axiom, it would seem obvious that this would result in rapid "evolution" of our crops. For several decades this was the main thrust of crop improvement research. Vast numbers of mutants were produced and screened, collectively representing many billions of mutation events. A huge number of small, sterile, sick, deformed, aberrant plants were produced. However, from all this effort, almost no meaningful crop improvement resulted. The effort was an enormous failure for the most part and was almost entirely abandoned. Why did this huge mutation/selection experiment fail even with a host of Ph.D. scientists trying to help it along? Because even with all those billions of mutations there were no significant new beneficial mutations arising. The several exceptions prove the point. Low phytate corn is the most notable example of successful mutation breeding. Such low phytate corn has certain advantages in terms of animal feed. The low phytate

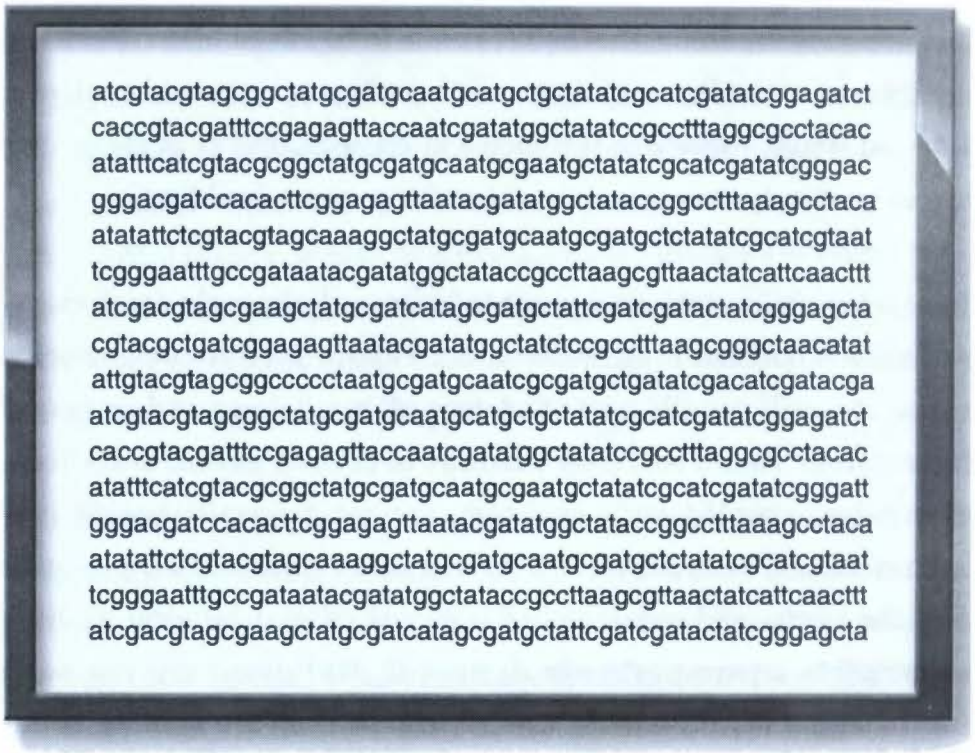
corn was created by mutatagenizing corn, and then selecting for strains wherein the genetic machinery which directs phytic acid production had been damaged. Although the resulting mutant may be desired for a specific agricultural purpose, it was accomplished through net loss of information (like the broken car alarm), and the loss of a biological function. Most of the other examples of successful mutation breeding are found within the area of ornamental plants, where dysfunctional anomalies are found to be novel and interesting to the eye. Examples of "useful" mutations within ornamental plants include sterility, dwarfing, mottled or variegated foliage, or misshaped floral organs.

If essentially no truly positive mutations (resulting in a net gain of information) could be recovered from this vast science-guided process, why do we think the identical process, in the absence of any guiding intelligence, would be more fruitful in nature? However, the very same scientists who failed at mutation/selection were *extremely* successful in crop improvement when they abandoned mutation breeding and instead used the pre-existing natural variation within each plant species or genus. This would make sense if such pre-existing variation did not principally arise via mutation, but originally arose by *design.*

Bergman (2004) reviewed the topic of beneficial mutations. Among other things, he did a simple literature search via Biological Abstracts and Medline. He found 453,732 "mutation" hits, but among these only 186 mentioned the word "beneficial" (about 4 in 10,000). When those 186 references were reviewed, the presumed beneficial mutations were only beneficial in a very narrow sense and consistently involved *loss-of-function* (loss of information)

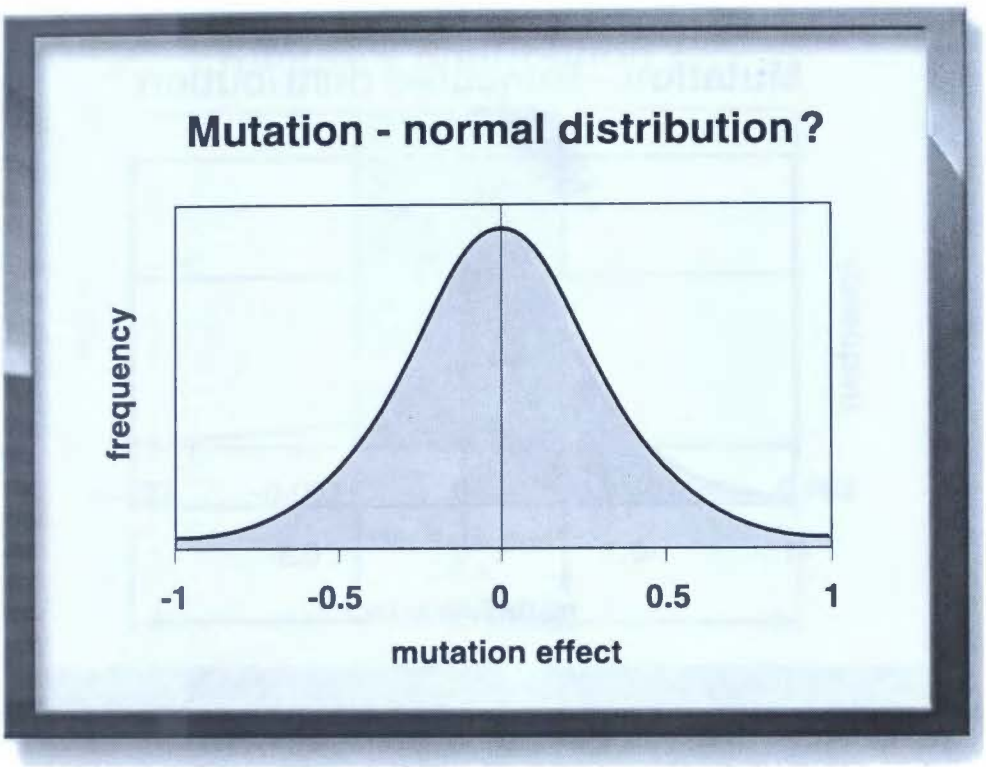
changes. He was unable to find a single example of a mutation which unambiguously created new information. While it is almost universally accepted that beneficial, information-creating mutations *must* occur, this belief seems to be based upon uncritical acceptance of the Primary Axiom rather than upon actual evidence. I do not doubt there *are* beneficial mutations, but it is clear they are exceedingly rare–much too rare for genome-building.

In conclusion, mutations appear to be overwhelmingly deleterious, and even when one may be classified as beneficial in some specific sense, it is still usually part of an over-all breakdown and erosion of information. As we will soon examine in greater detail, mutations, even when coupled with selection, cannot generally create new information. The types of variation created by mutation are more like the dings and scratches of life, and cannot be seen as life's spare parts (spare parts are designed). Mutations are the basis for the aging of individuals, and right now they are leading to our death, both yours and mine. Unless selection can somehow stop the erosion of information in the human genome, mutations will not only lead to our personal death, they will lead to the death of our species. We will soon see that natural selection must be able to simultaneously select against extremely large numbers of nearly-neutral nucleotide mutations in order to prevent genomic degeneration.




## *Figure 2.*

The genome appears to us as a linear array of letters: A, T, C, G. The actual genome is 3 million fold greater than the sequence shown above. To view just half of your own genome, you would have to view 10 nucleotides every second, for 40 hours per week, for 40 years! The apparent simplicity of this language system is deceptive. A higher genome, almost certainly, must comprise a great deal of data compression (see Chapter 9), as well as a great deal of non-linear information. Except for certain short portions, we cannot view the genome as simply a linear text, like a book. Much of the information content is probably found in 3-dimensional structures, as is the case with folded proteins.




## *Figure 3a.*

The naive view of mutations would be a bell-shaped distribution, with half of all mutations showing deleterious affects on fitness (left of center), and half showing positive effects on fitness (right of center). With such a distribution it would be easy to imagine selection removing bad mutations and fixing good mutations, inevitably resulting in evolutionary progress. However, we know this is a false picture.

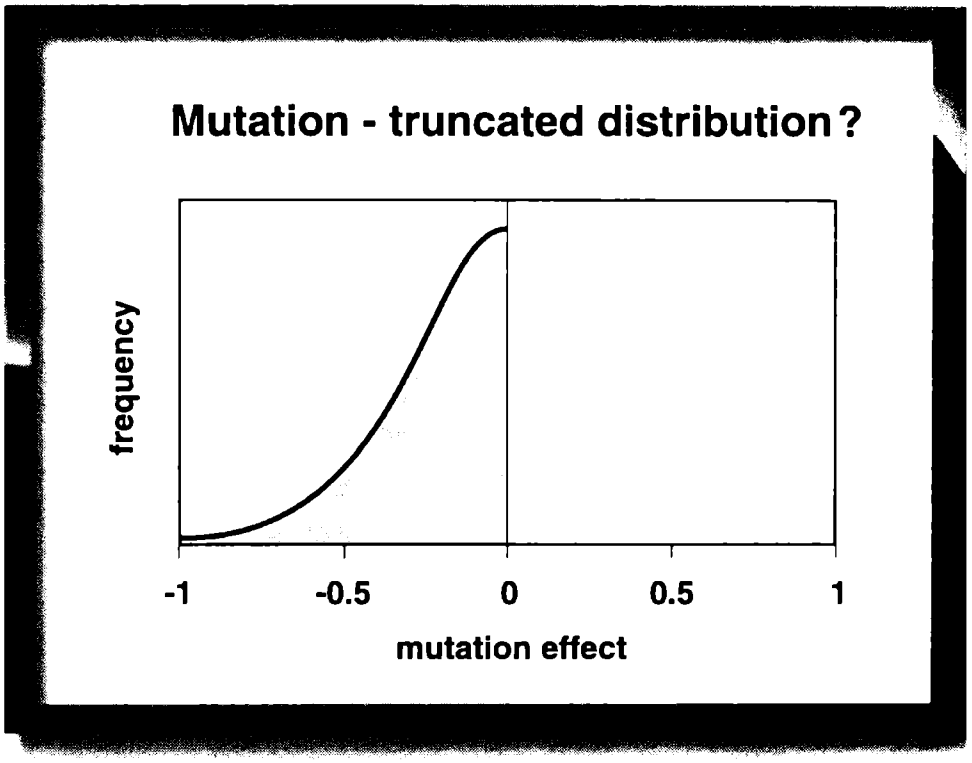
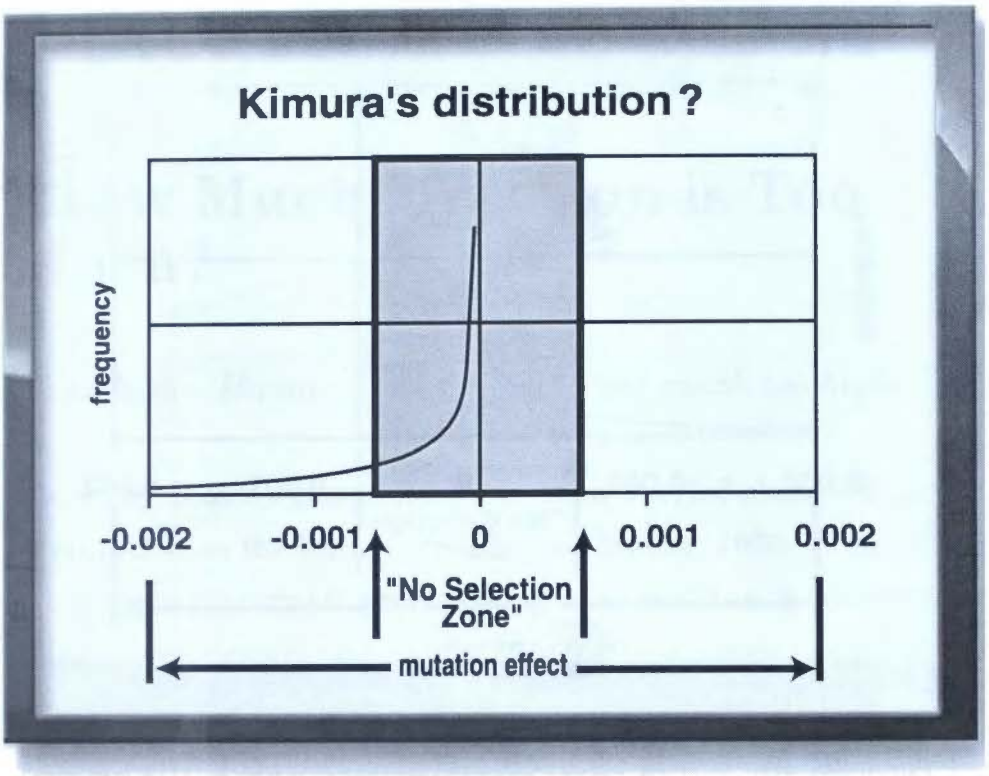



*Figure 3b.*

Population geneticists know that essentially all mutations are deleterious, and that mutations having positive effects on fitness are so rare as to be excluded from such distribution diagrams. This creates major problems for evolutionary theory. But this picture is still too optimistic.

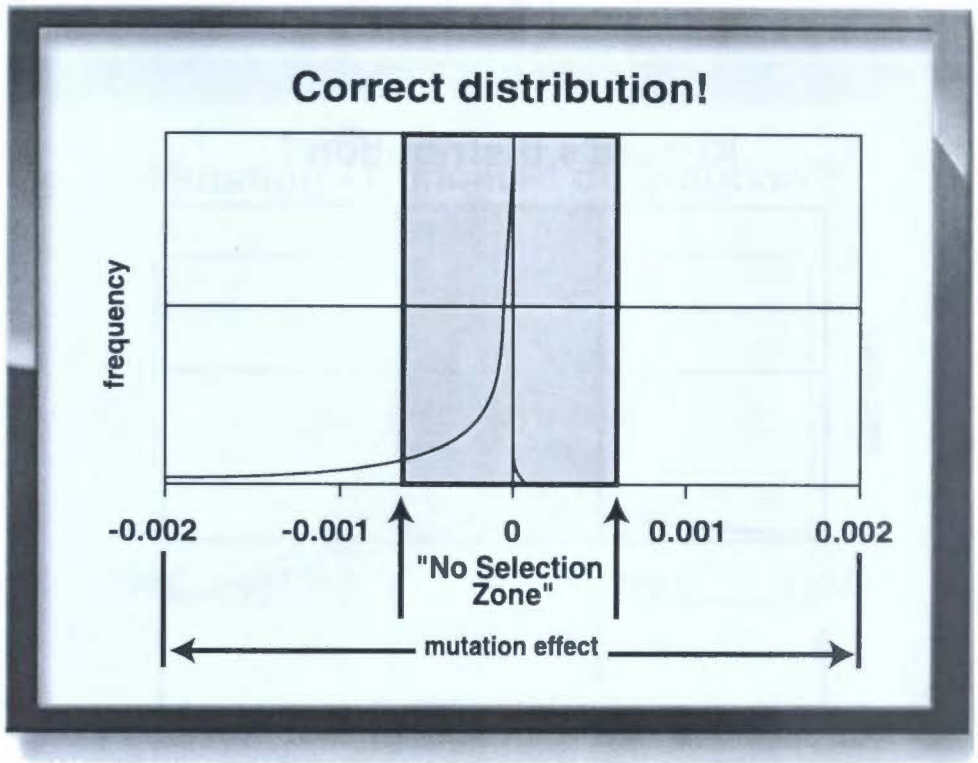



## *Figure 3c.*

Population geneticists know that mutations are strongly skewed toward neutral. Just like in an instruction manual, a few misspellings will be lethal but most will be *nearly harmless*. The nearly-neutral mutations create the biggest problems for evolutionary theory. This diagram is adapted from a figure by Kimura (1979). Kimura is famous for showing that most mutations are nearly neutral, and therefore are not subject to selection. Kimura's "no-selection zone" is shown by the box.

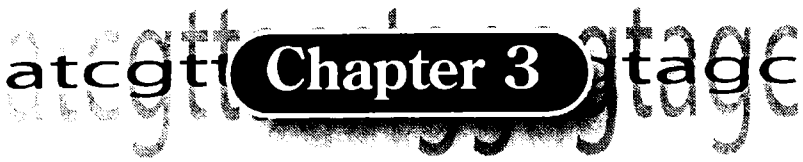
*The general shape of this curve is important, but the precise mathematical nature of this curve is not. While Ohta feels the mutation distribution is exponential, Kimura feels it is a 'gamma' distribution (Kimura, 1979). However, regardless of which specific mathematical formulation best describes the natural distribution of mutation effects, they all approximate the picture shown above.*

*For your possible interest, geneticists agree that the frequency of highly deleterious mutations is almost zero (not shown, off the chart), while "minor" mutations are intermediate in frequency (i.e., the left portion of chart, and off chart). Minor mutations are believed to outnumber major mutations by about 10-50 fold (Crow, 1997), but near-neutrals vastly outnumber them both.*




## *Figure 3d.*

Kimura's Figure (3c) is still not complete. To complete the figure we really must show where the beneficial mutations would occur, as they are critical to evolutionary theory. Their distribution would be a reverse image of Kimura's curve, but reduced in range and scale, by a factor of somewhere between ten thousand to one million. Because of the scale of this diagram, I cannot draw this part of the mutation distribution small enough, so a relatively large triangle is shown instead. Even with beneficial mutations greatly exaggerated, it becomes obvious that essentially all beneficial mutations will fall within Kimura's "no-selection zone". This completed picture, which is correct, makes progressive evolution on the genomic level virtually impossible.




# How Much Mutation is Too Much?

*Newsflash – Human mutation rates are much too high.*

For many decades geneticists have been worried about the impact of mutation on the human population (Muller, 1950; Crow, 1997). When these concerns first arose, they were based upon an estimated rate of deleterious mutation of *0.12 to 0.30 mutations per person per generation* (Morton, Crow and Muller, 1956). Since that time there have persisted serious concerns about accumulating mutations in man, leading to a high "genetic load" and a generally degenerating population. There has also been a long-standing belief that if the rate of deleterious mutations approached *one deleterious mutation per person per generation*, long-term genetic deterioration would be a certainty (Muller, 1950). This would be logical, since selection must eliminate mutations as fast as they are occurring. We need to prevent mutant individuals from reproducing, but we also need to leave enough remaining people to procreate and produce the next generation. By this thinking, deleterious mutations in man must actually be kept below one mutation for every three children if selection is to eliminate all the mutations and still allow the population to reproduce. This is because global fertility rates are now less than 3 children for every 2 adults, so only one child in three could theoretically be selectively eliminated. For these

reasons, geneticists have been naturally very eager to discover what the human mutation rate really is!

One of the most astounding recent findings in the world of genetics is that the human mutation rate (just within our reproductive cells) is at least 100 nucleotide substitutions (misspellings) per person per generation (Kondrashov, 2002). Other geneticists would place this number at 175 (Nachman and Crowell, 2000). These high numbers are now widely accepted within the genetics community. Furthermore, Dr. Kondrashov, the author of the most definitive publication to date, has indicated to me that 100 was only his *lower estimate.* He believes the actual rate of point mutations (misspellings) per person may be as high as 300 (personal communication). Even the lower estimate, 100, is an amazing number, with profound implications. When an earlier study revealed that the human mutation rate might be as high as *30,* the highly distinguished author of that study concluded that such a number would have *profound* implications for evolutionary theory (Neel et al., 1986). But the actual number is now known to be 100-300! Even if we were to accept the lowest estimate and further assumed that 97% of the genome is perfectly neutral junk, this would still mean that at least three additional deleterious mutations are occurring per person per generation. So *every one* of us is a mutant, many times over! What type of selection scheme could possibly stop this type of loss of information? As we will see, given these numbers, there is no realistic method to halt genomic degeneration. Since the portion of the genome that is recognized as being truly functional is rapidly increasing, the number of mutations recognized as being actually deleterious is also rapidly increasing. If the genome proves to be mostly or

entirely functional, then every one of these 100 mutations per person is actually deleterious. Yet even this number is too small. First, because it is only the lowest estimate, and second, because it only considers point mutations (misspellings). Not included within this number are the many other types of common mutations, such as deletions, insertions, duplications, translocations, inversions, and all mitochondrial mutations.

To appreciate the extent of this underestimation of the mutation problem, we should first consider the types of mutation that fall outside the normal point mutation counts. Then we need to consider what portion of the whole genome is truly functional.

Within each cell are sub-structures called mitochondria, which have their own small internal genome (about 16,500 nucleotides), which is inherited only through the mother. However, because the mitochondrial genome is highly polyploid (hundreds of copies per cell), and because the mitochondrial mutation rate is extremely high, there are still a large number of mitochondrial mutations that must be eliminated each generation in order to halt degeneration. The human mitochondrial mutation rate has been estimated to be about 2.5 mutations, per nucleotide site, per million years (Parsons et al., 1997). Assuming a generation time of 25 years and a mitochondrial genome size of 16,500, this approaches *one mitochondrial mutation per person per generation within the reproductive cell line.* Mitochondrial mutations, just by themselves, may put us over the theoretical limit of selective elimination. Even if the mutation rate is only 0.1 per person, we would have to select away a very substantial portion (10%) of the human population, every generation, just to halt mitochondrial

genetic degeneration. Yet this would still allow the 100-300 nuclear mutations per person per generation to accumulate unabatedly. High rates of mitochondrial mutation are especially problematic in terms of selection (Chapters 4 and 5), because of a lack of recombination ("Muller's ratchet"–Muller, 1964), and a lower effective population size (only women pass on this DNA, so selection can only be applied to half the population).

The most rapidly mutating regions of the human genome are within the very dynamic micro-satellite DNA regions. These unique regions mutate at rates nearly 1 million-fold above normal, and are not included in normal estimates of mutation rate. Yet these sequences are found to have biological impact, and their mutation results in many serious genetic diseases (Sutherland and Richards, 1995). It is estimated that for every "regular" point mutation, there is probably at least one micro-satellite mutation (Ellegren, 2000). This effectively doubles the mutation count per person per generation from 100-300 to 200-600.

In addition to nuclear point mutations, mitochondrial mutations, and micro-satellite mutations, there are a wide variety of more severe chromosomal mutations generally called "macro-mutations". These include deletions and insertions. According to Kondrashov (2002), such mutations, when combined, add another four (macro-) mutations for every 100 point mutations. This estimate appears to consider only the smallest of macro-mutations, and excludes the insertions/deletions affecting larger regions of DNA. Although there may be relatively few such mutations (*only* 4-12 per person per generation), these "major" mutations will unquestionably cause much more genomic damage, and so would demand

higher priority if one were designing a selection scheme to stop genomic degeneration. Macro-mutations can affect any number of nucleotides–from one to one million–even as we might accidentally delete a letter, a word, or even an entire chapter from this book. These relatively few macro-mutations are believed to cause three- to ten-fold more sequence divergence than all the point mutations combined (Britten, 2002; Anzai, 2003). This raises our actual mutation count to between 204 and 636 mutations per person per generation. But if we factor in the fact that macro-mutations can change three- to ten-fold more nucleotides than all point mutations combined, our final tally of nucleotide changes per person could come up to as high as 612-6,360 per person per generation! These numbers are mind-boggling! Yet even these numbers may *still* be too low. We have not yet considered inversions and translocations. Furthermore, evolutionary theorists are now invoking extremely high inter-genic conversion rates, which could double these numbers again. Wow! Do you recall the beginning of this chapter, where we learned that the famous geneticist Muller considered that a human mutation rate of 0.5 per person or higher would doom mankind to rapid genetic degeneration? Although we do not know the precise human mutation rate, there is good reason to believe that there are more than 1,000 nucleotide changes in every person, every generation (see Table 1). To be exceedingly generous, for the rest of this book I will use the most conservative number being referred to in the literature today–"just" 100 mutations per person per generation, except where otherwise specified. However, please note that this is only a fraction of the true number, and this number excludes the most destructive classes of mutations.

Of all these mutations, what percent are truly neutral? In the last few years there has been a dramatic shift in the perceived

functionality of most components of the genome. The concept of junk DNA is quickly disappearing (Slack, 2006). In fact, it is the "junk" (non-protein-coding DNA) which appears to be *key* to encoding biological complexity (Taft and Mattick, 2003). The Taft and Mattick study strongly suggests that the more "junk" an organism has, the more advanced the organism is. So mutations within "junk" DNA can hardly be assumed to be neutral!

More than 50% of the human genome is now known to be transcribed into RNA (Johnson et al., 2005). At least half of this transcribed DNA appears to be *transcribed in both directions* (Yelin et al., 2003)! So all of this DNA is not only functional, much of it may be *doubly* functional. While only a small fraction of the genome directly encodes for proteins, every protein-encoding sequence is embedded within other functional sequences that *regulate* the expression of such proteins. This includes promoters, enhancers, introns, leader sequences, trailing sequences, and sequences affecting regional folding and DNA architecture. I do not believe any serious biologist now considers introns (which comprise most of a typical genic region) as truly neutral "junk". In fact, many of the most strongly *conserved* (essential and invariant) sequences known, are found within introns (Bejerano et al., 2004). While a typical protein-coding sequence may only be 3,000 nucleotides long or less, the typical gene that controls the expression of that protein can be in the range of 50,000 nucleotides long. Since there are 20,000 - 40,000 protein-encoding genes (estimates greatly vary), if we include all their associated nucleotides (50,000 per gene), the true complete genes could easily account for over 1.5 billion nucleotides. This is fully half the genome. In addition, a whole new class of genes has been discovered which do not encode proteins, but encode functional RNAs. Such genes have escaped recognition

in computer searches for protein-coding sequences, and so have been overlooked as true genes. But they are true genes, and they probably comprise a large part of the genome (Mattick, 2001; Dennis, 2002; Storz, 2002). They are just now being discovered within DNA regions that were previously dismissed as junk. In addition, two independent studies have shown extensive sequence functionality within the large regions *between* genes (Koop and Hood, 1994; Shabalina et al., 2001). Such regions had also previously been assumed to be junk. Pseudogenes, long considered dead duplicated genes, have recently been shown to be functional (Hirotsune et al., 2003; Lee, 2003). Pseudogenes seem to be designed to make regulatory RNA molecules (see Chen et al., 2004), rather than proteins, so they are not "dead fossils". As I will discuss in more detail elsewhere, there even appear to be diverse cellular functions for the much-maligned "selfish genes", sometimes called "parasitic DNA sequences", also called "transposable elements". These elements appear to have multiple and extremely important functions within the cell, including the control of chromosome pairing (Hakimi et al., 2002), and DNA repair (Morrish et al., 2002). Repetitive DNA , including satellite DNA, long considered junk, has been shown to be essential to genome function, and comprise such essential genomic structures as centromeres and telomeres (Shapiro and Sternberg, 2005). Lastly, there are fundamental genome-wide structural patterns, which virtually permeate every portion of the genome, such as isochores (GC-rich areas–Vinogradov, 2003), genome-wide "word" patterns (Karlin, 1998), and nucleosome binding sites (Tachida, 1990; Segal et al., 2006). These genome-wide patterns appear crucial to cell function, and suggest functionality throughout the entire genome. For example, nucleosome binding (crucial to chromosome structure and gene regulation) appears to be specified by dinucleotide

patterns that repeat every 10 nucleotides (Sandman et al., 2000). So, one-fifth of the genome may be functional and essential *just for the purpose of specifying nucleosome binding sites* (Tachida, 1990). **It is becoming increasingly clear that most, or all, of the genome is functional. Therefore, most, or all, mutations in the genome must be deleterious.**

On a per person basis, 100 mutations represent a loss of only a miniscule fraction of the total information in our vast genome. However, the real impact of such a high mutation rate will be at the population level, and is primarily expressed with the passage of time. Since there are six billion people in the world, and each person has added an average of 100 new mutations to the global population, our generation alone has added roughly 600 billion new mutations to the human race. If we remember that there are only three billion nucleotide positions in the human genome, we see that in our lifetime there have been about 200 mutations for every nucleotide position within the genome. Therefore, every possible point mutation that *could* happen to the human genome *has* happened many times over, just during our lifetime! Because of our present large population size, humanity is now being flooded by mutations like never before in history. The consequences of most of these mutations are not felt immediately, but will manifest themselves in coming generations.

**As we will see, there is no selection scheme that can reverse the damage that has been done during our own generation, even if further mutations could be stopped.** No amount of selection can prevent a significant number of these mutations from drifting deeper into the population and consequently causing permanent genetic damage. Yet our children's generation will add

even more new mutations, followed by the next and the next. This degenerative process will continue into the foreseeable future. We are on a downward slide that cannot be stopped.

When selection is unable to counter the loss of information due to mutations, a situation arises called "error catastrophe". If not rapidly corrected, this situation leads to the eventual death of the species–extinction! In its final stages, genomic degeneration leads to declining fertility, which curtails further selection (selection always requires a surplus population, some of which can then be eliminated each generation). Inbreeding and genetic drift then take over entirely, rapidly finishing off the population. The process is an irreversible downward spiral. This advanced stage of genomic degeneration is called "mutational meltdown" (Bernardes, 1996). Mutational meltdown is recognized as an immediate threat to all of today's endangered species. The same process appears to potentially be a theoretical threat for mankind. What can stop it?

*Author's note: In June of 2007 a large international consortium of genome scientists (under the name ENCODE) published their finds in a set of 29 scientific papers. These findings have stunned the genetics community (Kapranov et al., 2007). They show that the human genome is vastly more complex than they had expected, and that essentially all of the genome is transcribed–most of it in both directions. They conclude that most nucleotides are not only functional but are poly-functional, having multiple roles. This means that the genome's functionality exceeds 100% (most of both strands of the DNA are functional). In this light, no mutations should be considered "perfectly neutral", and essentially all mutations must be considered deleterious. This means that the real deleterious mutation rate in man is nothing less than staggering–well over 100 mutations per person per generation! This is more than an order of magnitude greater than was considered possible just five years ago.*

| Mutation Type | Mutations per Person | Nucleotides changed/person |
|---|---|---|
| 1. mitochondrial mutations[a] | <1 | <1 |
| 2. nucleotide substitutions[b] | 100-300 | 100-300 |
| 3. satellite mutations[c] | 100-300 | 100-300 |
| 4. deletions[d] | 2-6 (plus) | 300-3000 |
| 5. duplications / insertions[e] | 2-6 (plus) | 300-3000 |
| 6. inversions / translocations[f] | numerous | thousands? |
| 7. conversions[g] | thousands? | thousands? |
| **total/person/generation[h]** | **>1,000?** | **thousands!** |

## *Table 1.*

There are many types of mutations and each acts as sources of heritable genetic change. Unfortunately, every single class of mutation results in a net loss of information. Mitochondrial mutation is the least significant source of human mutation. It produces less than one new mutation per person. Yet even a fraction of one mitochondrial mutation per person has prompted one evolutionist to comment: "***We should increase our attention to the broader question of how (or whether) organisms can tolerate, in the sense of evolution, a genetic system with such a high mutational burden.*" (Howell et al., 1996).** Now, consider all the types of mutation combined!

[a] *Mitochondrial mutation rate estimates vary, but can approach 0.5 per person (Parsons et al., 1997).*

[b] *Nuclear substitutions are hard to measure, but Kondroshov (2002) has estimated 100 per person. In personal communication he has indicated this may actually be 300.*

[c] *Normal estimates of nucleotide substitutions would not include mutational hotspots such as microsatellites. Microsatellite mutation rates have been estimated to be roughly equal to all point mutations rates.*

[d,e] *Kondrashov (2002) estimated that deletions plus insertions occur at a combined rates of about 4-12% of the point mutations, or about 2-6% each. However, he seemed to limit his estimate to only small inserts and deletions, so the actual number may be higher. Because mutations and insertions can be very large, their total effect is believed to be 3-10 fold greater than all point mutations combined in terms of total nucleotides changed.*

[f] *The actual rate of chromosomal rearrangements is unknown. Evolutionary assumptions about the recent divergence of chimp and man require high rates of such changes. These changes can affect very large pieces of DNA, and so for the evolutionary scenario to work, many thousands of nucleotides, on average, must move in this way every generation.*

[g] *The actual rate of inter-genic conversion is unknown, but evolutionary assumptions require extremely high rates of gene conversion between different loci–many thousands per person per generation.*

[h] *The total number of mutations can only be estimated in a very crude way, but it should be very clear that the number of all types of new mutations, including conversions, must be over 1,000 per person. These mutations, which include many macro-mutations, must clearly change many thousands of nucleotides per person per generation.*

atcgt Chapter 4 tagc

# All-Powerful Selection to the Rescue?

*Newsflash - Selection capabilities are very limited.*

The consensus among human geneticists is that, at present, the human race is genetically degenerating due to rapid mutation accumulation and relaxed natural selection pressure (Crow, 1997). These geneticists realize that there is presently a net accumulation of mutations in the population and that it is occurring at a much higher rate than was previously thought possible. Geneticists widely agree that these mutations are essentially either neutral or deleterious (if any are beneficial, they are considered so rare as to be entirely excluded from consideration). Subsequently, they realize that genetic information is currently being lost, which must eventually result in reduced fitness for our species. This decline in fitness is believed to be occurring at 1-2% per generation (Crow, 1997) (see Figure 4, p. 65). All this is happening on the genetic level, even though medical and technical advances are increasing our average life spans on the social level. Hence human geneticists would probably all agree that selection must eventually be increased if we are to stop genetic degeneration. However, there are essentially no public statements to this effect–imagine the profound political ramifications of such statements!

This acknowledged problem raises an interesting question: How much selection would be required to completely halt genetic degeneration? Or perhaps the question should really be this: Can such degeneration be halted at all?

For many people, including many biologists, natural selection is like a magic wand. There seems to be no limit to what one can imagine it accomplishing. This extremely naive perspective toward natural selection is pervasive. Even as a plant geneticist, I had an unrealistic conception of how selection was really operating in nature, and I had a very naive idea about how selection might work at the level of the whole genome. For the most part, the only scientists who have actually seriously analyzed what selection can and cannot do on the genomic level are a small number of population geneticists (an exceedingly specialized group). Population genetics is a field that is extremely theoretical and mathematical. Theoretical mathematicians are completely constrained by their *axioms* (assumptions), upon which they build their work. The entire field of population genetics was developed by a small, tightly knit group of people who were utterly and radically committed to the Primary Axiom. Today, it is still a very small field, still exclusively populated by "true believers" in the Primary Axiom. These people are extremely intelligent, but are totally and unconditionally bound to the Primary Axiom. For the most part, other biologists do not even understand their work and accept their conclusions by faith. Yet it is these *same* population geneticists themselves who have exposed some of the most profound limitations of natural selection (see Appendix 1). Because natural selection is *not* a magic wand but is a very real phenomenon, it has very real capabilities and very real *limitations*. It is not all-powerful.

### The Most Basic Problem – The Princess and the Nucleotide Paradox

Natural selection has a fundamental problem. It involves the enormous chasm that exists between **genotypic change** (a molecular mutation) and **phenotypic selection** (on the level of the whole organism). There needs to be selection for billions of almost infinitely subtle and complex genetic differences on the molecular level. But this can only be done by controlling reproduction on the level of the whole organism. When Mother Nature selects for or against an individual within a population, she has to accept or reject a complete set of 6 billion nucleotides–all at once! It's either take the whole book or have nothing of it. In fact, Mother Nature **never sees the individual nucleotides.** She sees the whole organism. She never has the luxury of seeing, or selecting for, any particular nucleotide. We start to see what a great leap of faith is required to believe that by selecting or rejecting a whole organism, Mother Nature can precisely control the fate of billions of individual misspellings within the assembly manual.

The problem of *genotypic change* versus *phenotypic selection* is very much like the problem of the children's story, *The Princess and the Pea*. The royal character of the Princess is discovered by the fact that she cannot sleep because, even through 13 mattresses, she feels a pea beneath her bed. Children are entertained by this story because it is so silly. Royalty or not, no one can feel a pea through 13 mattresses! But our genetic problem is actually a much more difficult situation. Our Princess (natural selection) essentially needs to read extensive books written in Braille through a set of mattresses in order to precisely identify which books have the fewest errors in them! It makes a great fairy tale, but who would

believe it as the underlying process which explains life? This whole problem can be called the *Princess and the Nucleotide Paradox*, which is whimsically illustrated in Figure 5 (p. 66).

To be fair, there are a few mutations that have a much bigger effect than a single Braille letter in our example. A few rare mutations have profound biological effects, acting more like a bowling ball under the mattress. Natural selection against these types of major mutations is an obvious no-brainer. But the bowling ball (semi-lethal) mutations are extremely rare, and such nucleotides carry only a miniscule amount of the total information in the genome. Most of the information in the genome is carried by nucleotides whose effects are actually much more subtle than even the Braille letters in our example. It is the origin and maintenance of all *those* nucleotides that we are trying to understand.

The gap between molecules and the whole organism is profound. Part of this gap involves size. If we were to make a nucleotide as big as a pea, a proportionately-sized Princess would be roughly 10,000 miles tall. Moreover, standing between a nucleotide and an individual organism are many different *levels of organization*. For example, a single nucleotide may affect a specific gene's transcription, which may then affect mRNA processing, which may then effect the abundance of a given enzyme, which may then affect a given metabolic pathway, which may then affect the division of a cell, which may then affect a certain tissue, which may then affect the whole organism, which may then affect the probability of reproduction, which may then affect the chance that that specific mutation gets passed on to the next generation. Massive amounts of uncertainty and dilution are added at each organizational level,

resulting in massive increase in "noise", and loss of resolution. There must be a *vanishingly small* correlation between any given nucleotide (a single molecule), and a whole organism's probability of reproductive success! The nucleotide and the organism are very literally worlds apart. Our Princess (natural selection on the level of the whole organism), has to perceive differences which are just above the *atomic level.*

We do not generally see individual pixels on our television, so imagine the difficulty of trying to select a specific TV set at the store by trying to evaluate the quality of each separate pixel, by eye, on all the various TV sets available. But it's really much worse than this. In a biological system, we are talking about pixels, within pixels, within pixels, within pixels. We are talking about a very long chain of events separating the direct effect of a given nucleotide and very remote consequences on the whole organism level. There is a logarithmic dilution at each step. At each level there is an order of magnitude loss of resolution and correspondence. It is like measuring the impact of a butterfly's stroke on a hurricane system a thousand miles away. It is a little like trying to select for a specific soldier, based upon the performance of his army. This whole picture is totally upside down! Yet this is the essence of the Primary Axiom! The Primary Axiom sees a human genome (6 billion nucleotides), and imagines that each unit is selected for (or not) individually, merely based upon a limited amount of reproductive sieving on the level of the whole organism. As we will see, this is impossible for many reasons.

To better understand the nature of The Princess and the Nucleotide Paradox, let's imagine a new method for improving textbooks. Start

with a high school biochemistry textbook and say it is equivalent to a simple bacterial genome. Let's now begin introducing random misspellings, duplications, and deletions. Each student, across the whole country, will get a slightly different textbook, each containing its own set of random errors (approximately 100 new errors per text). At the end of the year, we will test all the students, and we will only save the textbooks from the students with the best 100 scores. Those texts will be used for the next round of copying, which will introduce new "errrors", etc. Can we expect to see a steady improvement of textbooks? Why not? Will we expect to see a steady improvement of average student grades? Why not?

Most of us can see that in the above example, essentially **none** of the misspellings in the textbook will be beneficial. More importantly, there will be no meaningful correlation between the subtle differences in textbooks and a student's grade. Why not? Because every textbook is approximately equally flawed, and the differences between texts are too subtle to be significant in light of everything else. What do I mean by "everything else"? I mean that a student's grade will be determined by many other important variables, including different personal abilities and different personal situations (teachers, classrooms, other kids, motivation, home life, romantic life, lack of sleep, "bad luck", etc.). All these other factors (which I will call *noise*) will override the effect of a few misspellings in the textbook. If the student gets a high grade on the test, it is not because his text had slightly fewer errors, but primarily for all those other diverse reasons.

What will happen if this mutation/selection cycle continues unabated? The texts *will* obviously degenerate over time, and average student scores *will* eventually also go down. Yet this absurd

mutation/selection system is a very reasonable approximation of the Primary Axiom of biology. It will obviously fail to improve or even maintain grades for many reasons. The most fundamental reason why this type of selection fails is the incredibly weak relationship between individual letters in the text and the overall performance of the student. The correlation will be essentially zero. Therefore, this is an excellent illustration of the Princess and the Nucleotide Paradox. If this scenario seems absurd to you, try to understand one more thing: The Primary Axiom claims this very same mutation/selection system is actually what *wrote the entire biochemistry textbook in the first place.* There was never any intelligent agent acting as author or even as editor.

The problem of the Princess and the Nucleotide Paradox becomes even greater when we understand the phenomenon of *homeostasis.* Homeostasis is the natural phenomenon wherein all living things *self-regulate* themselves as circumstances change. A good example would be warm-blooded animals in a cold climate. Homeostasis results from an incredibly complex network of sensors and regulators within each cell. Although it is too complex to explain in detail, it is universally agreed that it is both operational and highly effective in all life systems. The phenomenon of homeostasis is a little like having a super-duper, self-adjusting mattress. If a tennis ball is put beneath this mattress, the mattress will automatically adjust itself via a myriad of complex mechanical mechanisms to effectively level the sleeping surface. But in real biology, it is more like we have 13 self-adjusting mattresses, one on top of the other (homeostasis operates at every level of biological organization). This makes things much more difficult for our Princess, who needs to sense the pea (read the Braille) through the mattresses.

When Mendel's genetic principles were "rediscovered" almost 50 years after Darwin, geneticists realized that there must be large numbers of hereditary units segregating within any given population. They also soon realized they had a problem if the number of hereditary units was very large. Although they did not speak of it as such, it was essentially what I am now calling the Princess and the Nucleotide Paradox. The early population geneticists, who were all philosophically committed Darwinists, realized they had to devise a way to overcome the Princess and the Nucleotide Paradox in order to make Darwinian theory appear genetically feasible*. So they very cleverly transferred the *unit of selection* from the whole organism to the genetic unit (i.e., the gene or nucleotide). To do this they had to redefine a population as being nothing more than a "pool of genes". In this way they could claim real selection was operating at the level of the nucleotide within the gene pool and not really on the individual. Each nucleotide could be envisioned as being independently selected for, or against, or neither. This made it very easy to envision almost any evolutionary selection scenario, no matter how complex the biological situation. And this effectively removed the mattresses from under the Princess, as if she could suddenly feel each pea, and could even read each Braille letter directly! This was an incredibly effective way to obscure the entire problem. Indeed, Darwinism would have died very naturally at this point in time, except for this major intellectual invention (Provine, 1971).

* *"Haldane...intended..., as had Fisher...and Wright...to dispel the belief that Mendelism had killed Darwinism...Fisher, Haldane, and Wright then quantitatively synthesized Mendelian heredity and natural selection into the science of population genetics." (Provine, 1971).*

There is one serious problem with redefining the problem in this way–the new picture is categorically false. Populations are not even remotely like pools of genes, and selection is ***never, ever*** for individual nucleotides. To justify this radical new picture of life, the theorists had to axiomatically assume a number of things which were all known to be clearly false. For example, they had to assume that all genetic units could sort independently so that each nucleotide would be inherited independently, as though there were no genetic linkage blocks (totally false). Likewise, they had to assume no epistasis, as though there were no interactions between nucleotides (totally false). They also typically assumed essentially infinite population sizes (obviously false). They usually implicitly assumed unlimited time for selection (obviously false). And they generally assumed the ability to select for unlimited numbers of traits simultaneously (which we will show to be false). From the very beginning of population genetic theory, many unrealistic and unreasonable assumptions were needed to make the model appear even feasible.

On this false foundation were built the theoretical pillars of modern population genetics. The models did not match biological reality, but these men had an incredible aura of intellectual authority, their arguments were very abstract, and they used highly mathematical formulations which could effectively intimidate most biologists. Furthermore, most biologists were also committed Darwinists and so were in philosophical agreement with the population geneticists. They were more than happy to go along for the ride even if the story did not quite make sense. In fact, the early population geneticists quickly became the idolized "darlings of science". I remember my own graduate-level classes in population

biology, and my own naive and meek acquiescence in accepting the very unnatural redefinition of life as "pools of genes". I remember not quite getting it, and assuming the problem was just with me (although all the other students in my class seemed to have the same problem). Since I *knew* evolution was true, it did not really matter if I was not *quite smart enough* to really grasp the idea of life as pools of nucleotides. If the gurus of population genetics were saying it was true, who was I to argue? Even if their premises were false (such as independent assortment of nucleotides), their conclusions must still doubtless be true–they were geniuses! Even though I was actually one of the more free-thinking students, I still swallowed the Princess and the Nucleotide story with essentially no resistance.

What is the biological reality, apart from ideology? The reality is that selection acts on the level of the organism, not on the level of the nucleotide (see Crow and Kimura, 1970, p. 173). Human genes never exist in "pools". They exist in massive clusters within real people. Each nucleotide is intimately associated with all the other nucleotides within a given person, and they are only selected or rejected as a set of 6 billion. The phenomenon of linkage is profound and extensive, as we will see. No nucleotide is ever inherited independently. Each nucleotide is intimately connected to its surrounding nucleotides, even as each letter on this page is specifically associated with a specific word, sentence, paragraph, and chapter. This book was not produced by a selective system like a giant slot machine where each letter is selected randomly and independently. Each letter was put in place by design, as part of something greater, as part of a specific word, a sentence, a paragraph and a chapter. This is also true of nucleotides. They only

exist and have meaning in the *context* of other nucleotides (which is what we call epistasis). We now know that human nucleotides exist in large linked clusters or blocks, ranging in size from 10,000 to a million. These linkage blocks are inherited as a single unit and never break apart. This totally negates one of the most fundamental assumptions of the theorists, that each nucleotide can be viewed as an individually selectable unit. Since the population genetics model of life (as pools of genes) is categorically false, the Princess and the Nucleotide Paradox remains entirely unresolved. This should be an enormous embarrassment to the entire field of population genetics. On a practical level, it means natural selection can never create, or even maintain, specific nucleotide sequences.

Not only is the Princess and the Nucleotide Paradox unresolved, we now know that the problem is vastly worse than the early population geneticists could have imagined. We have now learned that the size and complexity of the genome (the extent of the Braille books) is vast, that homeostasis (the thickness of the mattresses) is extensive, and there are many more levels of organization (the number of mattresses) separating the genotype from the phenotype. We will have to wait until Chapter 6 to fully understand the problem of biological "noise" (it turns out the mattresses themselves are full of pea-sized lumps). So we should be able to see that the Princess and the Nucleotide Paradox is a show-stopper. The Primary Axiom fails at this first and most basic level. Any child should be able to see it, although many adults are "too well educated" to see it. Yet the paradox of the Princess and the Nucleotide is just the beginning of the problems the Primary Axiom has. For the purpose of further discussion, and for the rest of this book, I will be happy to give the theorists their model of life

as "pools of genes" and the idea of selection on the level of single nucleotides. I agree to do this because, as we will see, there are many other problems which fully discredit the Primary Axiom. For the record, the Princess and the Nucleotide Paradox is in itself sufficient basis for rejecting the Primary Axiom (see Appendix 3).

## Three Specific Selection Problems

To understand the basic issues of genomic selection (which will soon become fairly complex), let us look at this question using a simple case. Imagine a single point mutation that has accumulated within the human population, to the extent that 50% of all people bear this mutation. What type of selection is required to eliminate this mutation, and what are the critical factors? For simplicity, we will be assuming the mutation is dominant (almost all mutations are recessive, which makes selection much more difficult). At first glance, the problem seems very easily solved. We could eliminate all these mutants in a single generation if we could afford to lose 50% of the breeding population, if we could clearly identify every person carrying the mutation, and if we could prevent 100% of the carriers from reproductive mating. So what are the problems?

**1. Cost of selection.** The problem of the "cost of selection" was first described by Haldane (1957), and later validated and expanded upon by Kimura and Ohta (1971), and Kimura (1983). It has been further clarified by ReMine (1993, 2005). All selection involves a biological *cost*, meaning that selection must remove ("spend") part of the breeding population. This is the essence of selection! In the current example, we should ask, "Can we really afford to spend 50% of humanity, preventing half the people from reproducing, so that we can make rapid selective progress?" Given humanity's

fertility levels (globally less than 3 children for every 2 adults), if we eliminate 50% of our population for the purpose of selection, the population size will be reduced by 25%. Obviously, each pair of adults need to have at least two reproducing children to maintain the population size. Furthermore, not all children will go on to reproduce (for reasons like accidental death, personal choice, etc.). Therefore, considerably more than two children for every two adults are needed to keep the population viable. Given our low fertility, if three children per two adults were needed for population continuity, zero selection would be possible. For these reasons, substantially less than one child in three is available to be "spent" for selection purposes. Haldane (1957) believed that only 10% of a typical natural human population could realistically be spent for selection purposes. If 50% of the population *was* removed for purposes of selection every generation, the human population would shrink rapidly, eventually leading to our extinction. Therefore, in the above example, elimination of all the mutant individuals in one generation is not reasonable. However, doing this same amount of selection in two generations *might* be reasonable since only 25% of the population would be spent for selection, per generation.

The purpose of this simple illustration is to show that while selection works, there are clear limits in terms of how intense our selection can be, and we must understand that every selective event has a biological cost. This becomes a major issue when selecting against many different mutations simultaneously. For the human population, it becomes clear that the maximum part of our population that can be "spent" for all selection purposes is considerably less than 33%, and, according to Haldane, might realistically be in the range of 10%. In contrast, while I was a plant

breeder at Cornell University, I could easily "spend" (eliminate) 99% of my breeding populations for selection purposes because of the extreme fertility of plants.

The concept of "cost of selection" is so important that I need to say more about it. The normal reproductive rate of a species must obviously be at least two offspring for every two adults or the species quickly goes extinct. However, every species needs much more reproduction than this just to survive. An *excess* population is needed to "fund" many things, both genetic and non-genetic. For example, there is a huge *random* element to successful reproduction. Many individuals in a population die or fail to reproduce for reasons that have nothing to do with genetics. Being hit by a truck or killed in a war has very little to do with a person's genetic "fitness". This cost of random death is absolute, and must be "paid" before we even consider selection. In some species, this cost may be 50% or more of the total population. In such cases, we need at least 4 offspring per 2 adults just to avoid extinction. But at this point, selection has not yet even begun. When we actually consider the genetic factors that determine reproductive success, there are significant genetic features which are *not* passed on to the offspring. These genetic components are not "heritable". For example, many genes work well in *certain combinations*, but are undesirable all by themselves (this would be true wherever there is *heterosis* or *epistasis*). Selecting for such gene combinations is really "false selection", because it does the offspring no good. The gene combinations are broken up in meiosis and are not passed on. Yet such "false selection" must still be paid for, requiring still more reproduction. And we have not yet started to pay for "real" selection! Real selection can take several forms: stabilizing selection, sexual

selection, progressive selection, etc. Each form of selection has a reproductive cost. All reproductive costs are additive, and **all costs must be paid for**. Total reproductive costs must never exceed the actual reproductive potential of a species. Only if a species is sufficiently fertile, and there is sufficient surplus population to fund **all other costs**, does any type of selection become feasible. In other words, selection is only possible to the extent that there is residual excess population, after all other costs have first been paid. Selection is a little like discretionary spending for a family on a tight budget. The question always comes down to, "Can we afford it?"

*Fitness* (due to phenotypic superiority) is actually the real trait that natural selection always acts upon, and this very fundamental trait is actually *very poorly inherited.* This runs counter to popular thinking. According to Kimura, fitness has low *heritability*, perhaps as low as 0.004 (Kimura, 1983, p.30-31). The concept of heritability is dealt with in more detail in Chapter 6. For now it is sufficient to know that low heritability means that environmental factors are much more important than genetic factors in determining who appears "superior". For Kimura to say that general fitness has very poor heritability is an amazing acknowledgment! It means that, even with intense selection pressure, nearly all of a population's surplus ends up being "spent" to remove non-heritable variations, and thus **most reproductive elimination is unproductive.** In other words selection for general fitness has minimal impact on the makeup of the next generation. Kimura's statement implies that *only a small fraction of the surplus population is truly available to pay for the elimination of mutations* (which is exactly what I have been saying). Despite this very important fact, I am going

to be exceedingly generous for now and will assign all available "selection dollars" (surplus population) to the elimination of mutations. Unless otherwise specified, I will assume that the entire surplus population is dedicated exclusively to selection for removal of mutations. However, the reader needs to understand that, in reality, only a very small fraction of any population's surplus can honestly be apportioned to mutation elimination (see Chapter 6, Figure 8a-c, pp. 100-103).

I believe one of the most fundamental mistakes that theorists make, as they invent their various scenarios, is to ignore selective cost. They spend their selection dollars like a teenager with a credit card. They speculate as if there is always an infinitely large surplus population. Because theorists are usually unconstrained by realistic cost limits, in their minds they imagine they can "fund" any number of simultaneous selection scenarios. They can spin off one selection scenario upon another. This reminds me of the old westerns where the cowboy would fire his "six-shooter" dozens of times without reloading, or like Legolas, in *Lord of the Rings,* who never runs out of arrows! However, such movies are fantasies, and the movie makers are free to claim "artistic license". Genetic theorists do not have artistic license, and should be held accountable for how they spend their selection dollars, even as an accountant would be held accountable for where the money goes. Theorists should be assigned a realistic number of selection dollars based upon the reproductive reality of a given species. They should then "spend" this part of their surplus population soberly, and without any deficit spending. If this principle were honestly employed, there would be greatly diminished expectations of what selection can really do.

**2. Recognizing obscured ("invisible") mutations.** If you want to select against a mutant, you must be able to identify it within the population. But we cannot identify the carriers of a typical point mutation apart from screening the whole population using very expensive DNA tests. Only those extremely rare point mutations which cause gross physical deformities can normally be identified on a practical level. For most individual point mutations, even though they are destructive and result in loss of information, they are so subtle that they are essentially "invisible". They do not produce a distinct or recognizable effect. To artificially select against a typical point mutation, we would need to do expensive lab analyses for every person on the planet, and this is entirely impractical. Therefore, we can see that there are fundamental problems in terms of identifying "good" versus "bad" individuals for selection. Obviously, when considering millions of mutations simultaneously, this problem becomes mind-boggling. Imagine wanting to buy an encyclopedia set, knowing that each set of volumes has its own unique collection of thousands of misspellings. Could you realistically stand there in the bookstore and sort through all those volumes with the expectation of finding the set of volumes which was least "degraded"? Given two sets, each of which contains its own unique set of 10,000 misspellings, how would you choose which set has the worst mistakes? The choice would become totally arbitrary! This issue of large numbers of silent or "nearly-neutral" mutations was first recognized by Kimura (1968), and its implications have been explored by Kondrashov (1995).

**3. Systematic reproductive elimination.** The cost of selection and "silent" mutations are huge problems. The challenge becomes even greater when it comes to preventing mutant individuals

from mating. Nowhere on this planet is there a social system that can control human reproduction with high precision. The most infamous example of this occurred in Nazi Germany under Hitler. But that experiment failed catastrophically. Planned Parenthood and modern birth control practices, while effective in reducing average family size, have not been effective in eliminating mutations. In most instances, human mating and reproduction remain essentially random, except for those very rare cases where mutations result in very pronounced genetic defects.

From our very modest illustration above, we must conclude that we are not in a practical position to artificially select for even one point mutation within the human population. This is very sobering news. When we then go on to consider multiple mutations, the problems escalate exponentially. Even if we were able to identify all the carriers of numerous mutations, and could effectively prevent them all from mating, we would still sooner or later encounter the problem of selective cost, because when we simultaneously try to select against multiple mutations we run into the problems inherent with a rapidly shrinking population size. So we begin to see that selection is not as easy as we thought! Even the simplest selection scenario requires several important factors: 1) maintenance of population size; 2) clear identification of mutants; and 3) effective exclusion of the mutants from the breeding population. As we will see more clearly in the next chapter, when we consider all mutations simultaneously each one of these three requirements becomes utterly impossible.

Will natural selection come to the rescue? After considering these problems, one possible conclusion might be to take no action and

let nature do it for us! The problem is that natural selection, like artificial selection, entails exactly the same problems. Natural selection, because of the cost of selection, cannot select against too many mutations simultaneously, or else selection will either become totally ineffective or will result in rapidly shrinking population sizes (or both). Furthermore, natural selection needs to be able to recognize multitudes of essentially invisible mutations. Lastly, natural selection needs to be able to somehow exclude multitudes of mutations from the breeding population, simultaneously, which is logistically impossible because of *selection interference*. These very real constraints on natural selection will limit what we can realistically expect natural selection to accomplish.

Genetic selection still works. Please do not misunderstand where I am going with this. I am not saying that selection does not work, for on a limited level it certainly does! My career as a plant breeder involved the use of artificial selection. My colleagues and I were able to regularly breed better plant and animal varieties which have had fundamental importance to modern agriculture. When I later became involved in genetic engineering of plants, we routinely used selection techniques to recover transgenic (genetically engineered) plants. Likewise, natural selection has eliminated the worst human mutations. If it had not, the human race would have degenerated long ago and we would not be here to discuss all this. But both natural and artificial selection have very limited ranges of operation, and neither has the **omnipotent power** so often ascribed to them. Selection is not a magic wand. While I will enthusiastically agree that selection can shape some specific gene frequencies, I am going to argue that no form of selection can maintain (let alone create!) higher genomes. The simplest way to

summarize all this is as follows: **Selection can sometimes work on the genic level, but systematically fails at the genomic level.**

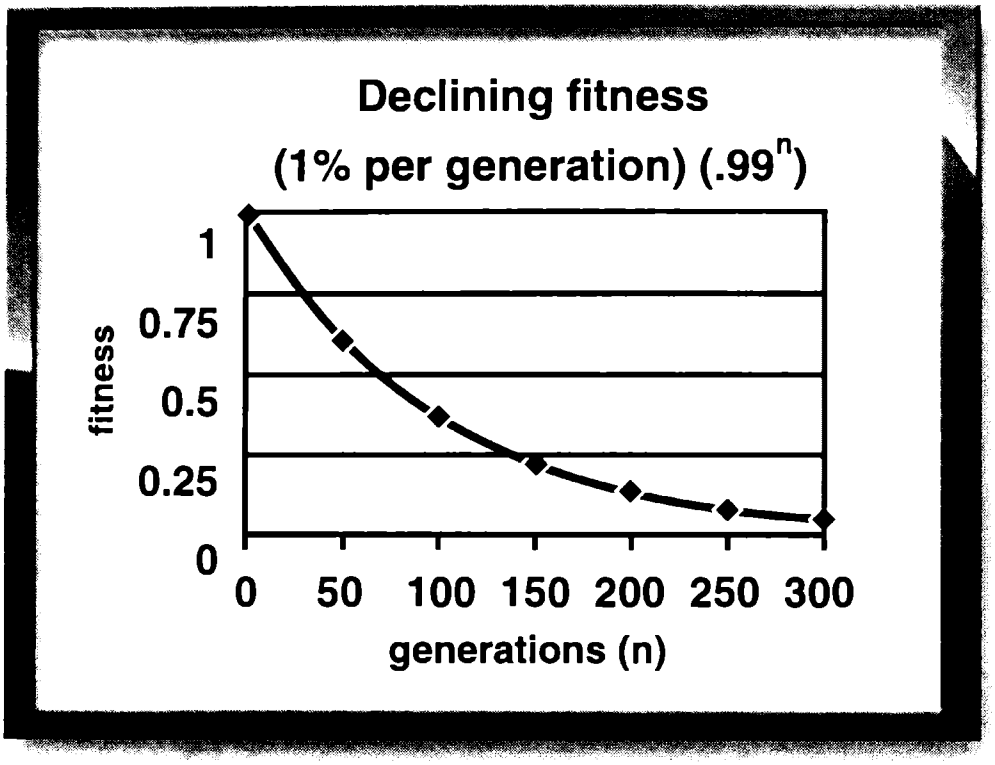



*Figure 4.*

Dr. Crow (1997) indicates that he believes the fitness of the human race is presently degenerating at 1-2% per generation due to the accumulation of mutations. A 1% decline in fitness per generation (beginning with a fitness of 1) is shown for a hypothetical human population over a period of 300 generations (6,000 years). This type of progressive loss of fitness would clearly lead to dramatic degeneration of the human race within the historical timeframe.

## *Figure 5: The Princess and the Nucleotide Paradox.*

The Primary Axiom requires that natural selection, which occurs on the level of an individual (the Princess), must recognize billions of individual nucleotide effects, which only exist on the molecular level (the peas). Separating the Princess and the nucleotides is a vast gulf. This gulf is partly due to separation in scale (to picture this, try to realize that if a nucleotide was as big as a pea, a human body would be roughly 10,000 miles tall.). This gulf is also the separation by level of organization (there are at least a dozen levels of biological organization between a nucleotide and a human being). No nucleotide affects a human body directly, but only through an elaborate labyrinth of nested systems. So the mattresses between the Princess and the nucleotide are many, and they are very thick. To make things still worse, life's self-correcting mechanism (called homeostasis) operates on every biological level, effectively silencing most nucleotide effects, even as modern sound-cancellation technologies use negative feedback to negate noise. For our analogy, we would have to incorporate high-tech internal "auto-correction" machinery into each mattress. But we have to add one more dimension to our analogy to make it accurate. The Primary Axiom does not just ask the Princess to sense if there is a single pea beneath her stack of mattresses. Through these mattresses she must "feel" encyclopedias written in molecule-sized Braille bumps, and decide which volumes have the fewest mistakes!


# Can Genomic Selection Problems Be Solved?

*Newsflash – Selection cannot rescue the genome.*

We began the last chapter by considering the problems associated with selecting for a single mutation within a human population. Traditionally, geneticists have studied the problem of mutations by simply considering one mutation at a time. It has then been widely assumed that what works for one mutation can be extended to apply to all mutations. Wow, talk about senseless extrapolation! This is like saying that if I can afford one car, I can afford any number, or if I can juggle three balls, I can juggle 300! We are learning that the really tough problems are not seen with single genes or with single nucleotides but arise when we consider all genetic units combined (the whole genome). To understand what is needed to prevent genomic degeneration, we must consider the problem of mutation on the genomic level, and we must implement what I am calling "genomic selection".

There are 3 billion nucleotide positions, each with two copies in the genome, and so there are 6 billion possible point mutations (misspellings). The profound difficulties of making mutation/ selection work on the genomic level have only been recognized by a few far-sighted geneticists in the past (e.g., Haldane,

Muller, Kimura, Kondrashov), but the whole sticky problem has repeatedly been swept under the rug. This is because it creates insurmountable problems for evolutionary theory. In the last few decades, we have learned that the genome is much larger and more complex than anyone predicted. We have learned that the human mutation rate is much higher than was previously thought possible. We are learning that the actual percentage of mutations that are truly neutral is steadily shrinking, and the percentage that actually *add* information is vanishingly small, if they exist at all. For all these reasons, we cannot ignore the problem of genomic degeneration any longer. We must ask, "Can *genomic selection* solve the problem?"

The bottom line is virtually every one of us is exceedingly mutant. This destructive mutation process has been going on for a long time. In addition to the roughly 100 new mutations we each have added to the human gene pool, we have inherited a multitude of mutations from our progenitors. To put the problem of genomic selection in proper perspective, we have to take the selection problem posed at the beginning of the last chapter (for a single point mutation at a single nucleotide site) and multiply this problem by a factor of at least one billion *(I am allowing that 2/3 of all nucleotide positions are "junk DNA", may be truly neutral, and thus would not need selection, even though it is not clear that any part of the genome is truly neutral).* Can you start to see that selection against mutations on the genomic level is fundamentally different from our first illustration where we were just selecting against a single mutation?

**1. Cost of selection.** The fact that all people are mutant makes selection much more difficult. If we were to select against all

mutations, no one could reproduce, resulting in instant extinction! Obviously this selection strategy creates a reproductive cost that is too high! It is widely acknowledged that we each inherit thousands of deleterious mutations. We carry many *trillions* of deleterious mutations collectively as a population. However, to make the problem easier, let's limit our attention to just the 600 billion new mutations that entered the human gene pool within our own generation. Since we cannot simply select against "mutants", we will have to select between individuals who are "more mutant" versus those who are "less mutant". As we will see, recognizing "more mutant versus less mutant" is a huge problem in itself. And all this selection must cost us considerably less than 33% of the population per generation if we are to survive.

Let me try to illustrate the extent of the cost problem associated with selecting against 600 billion mutations. If we have a population of 6 billion people, then only one third of them could be "eliminated" (prevented from having children) at maximum. This is 2 billion people. Try to imagine that. This thought should be enough to make even the most cold-blooded eugenicist shudder. Yet what good would this Draconian measure accomplish? Preventing 2 billion people from mating would only eliminate 100 x 2 billion = 200 billion new mutations. This would still leave 400 billion new mutations as the newly added *genetic burden* for the next generation! Even if we assume that two-thirds of the remaining mutations are perfectly neutral, we still have 133 billion deleterious mutations added to the population. We can't get rid of enough of the mutations and still maintain population size! Even if two-thirds of the mutations are neutral, and in addition we doubled selection intensity (although we certainly cannot afford to

"spend" two-thirds of our population), it would still leave 67 billion new deleterious mutations for the next generation. The cost of selection clearly limits how many mutations we can eliminate per generation, and the known mutation rate for humans is too high to be countered by any level of selection. Therefore, mutations will continue to accumulate, and the species must degenerate! Can you see that the cost of selection is rather a mind-boggling problem when viewed on the genomic level?

**2. Obscured or "invisible" mutations.** Surprisingly, when it comes to selection, lethal and near-lethal mutations are not the real problem, at least not from the whole population's point of view. Such mutations are rare and self-eliminating. Likewise, absolutely neutral mutations do not matter, if they exist at all. It is the minor mutations that do the most damage, especially within short time frames (Kimura and Ohta, 1971, p.53). Selection must prevent the accumulation of minor mutations or the species will rapidly deteriorate and fitness will decline. However, even if selection *could* keep minor mutations in check, it appears to be powerless to stop the accumulation of the most abundant class, *nearly-neutral* mutations. Therefore, higher genomes will eventually all degenerate in the long run, with or without selection.

**2a) Nearly-neutral mutations.** *Nearly-neutral mutations* have infinitesimally small effects on the genome as a whole. Mutations at all near-neutral nucleotide positions are automatically subject to random drift, meaning they are essentially immune to selection. Their fitness effects are so miniscule that they are masked by even the slightest fluctuations, or *noise*, in the biological system (Kimura, 1968; 1983; Kimura and Ohta, 1971). These are the most abundant mutations, as shown in the "near-neutral box" in Figure 3d (p. 32).

Since most mutations should be nearly neutral, and since they are so subtle as to avoid being selected for, why are they important? They matter because those nucleotide sites contain information, and their mutation contributes to the erosion of information. **Collectively, near-neutral nucleotides must account for most of the information in the genome.** This is just as true as the fact that all the seemingly insignificant letters in this book collectively add up to a clear message. If we start with a very long and complex written message (an encyclopedia, for example), and we start to introduce typographical errors, most of the individual errors will only have an extremely trivial effect on the total message. Individually they are truly insignificant. But if this process is not halted, the message will eventually become corrupted, and it will eventually be completely lost. An alternative example would be the rusting of a car. As a car ages we can repair the big stuff, replace tires, and fix dents (akin to selection for major and minor mutations), but we cannot stop the rusting process, which is happening one atom at a time (akin to near-neutral mutations). Each iron atom that oxidizes seems perfectly insignificant, but added up across the entire car, the process is certain and deadly. A third example would be the aging of our bodies. We can repair teeth, do facelifts, even replace hearts. But it is the cumulative aging of the individual cells (principally due to mutations) that places a specific limitation on our lifespan. This is true even though each individual cell is trivial and entirely expendable. Just as the human body "rusts out" due to countless microscopic mistakes (all of which in themselves are insignificant), the human genome must also be "rusting out" due to near-neutral mutations. No selection scheme can stop this process. This is the essence of the near-neutral mutation problem. This whole problem has led

one prominent population geneticist to write a paper entitled, "Why have we not died 100 times over?" (Kondrashov, 1995). The problem of the unselectability of near-neutrals is very real.

A large, homogeneous population in a homogenous environment (for example, a typical bacterial culture) is more resistant to genetic drift because it sees much less noise and experiences much more efficient selection. Such populations usually have simpler genomes, fewer mutations per genome, and far fewer inter-genic interactions. Furthermore, they exist in large numbers and have very high rates of reproduction. Most importantly, *every cell is subject to selection, independently, at every cell division.* Selection in such systems is more effective, more precise, and can have much higher resolution. This means that in bacteria, a much smaller proportion of the genome is near neutral and unselectable. This is why theorists typically prefer to use microbial examples.

Unfortunately, mammals such as ourselves have none of the advantages listed above. We are subject to high levels of reproductive noise. We have a large genome, high mutation rates, high levels of gene interaction, and we have very serious constraints on selection. This is why the proportion of mutations which are virtually "unselectable" should be very large in man, and the frequency of such mutations within the population should be entirely controlled by random genetic drift. All such nucleotide positions will mutate freely, and all information encoded by them will degenerate over time.

**2b) Selection threshold for too many minor mutations.** Minor mutations, by definition, have a small but distinct effect on

reproductive potential. These are the mutations immediately to the left of the near-neutral box, in Figure 3d (p. 32). While animal and plant breeders may have a hard time seeing these subtle changes, natural selection (which is really just another way of saying differential reproduction) can generally "see" them, since they affect reproductive probability by definition. Furthermore, the effects of such mutations are partly additive, so natural selection can select for *numerous* minor mutants simultaneously. In fact, the way natural selection works is very elegant and appears to be designed to stabilize life, which would otherwise very quickly deteriorate. It is really a very wonderfully designed system.

However, selection for minor mutations has significant limitations. The orderly elimination of minor mutations is seriously disrupted by noise. Natural selection must *see* the mutants as a significant factor in reproductive probability. But "Mother Nature" can have trouble seeing minor mutations. This is because the differences in reproductive fitness caused by minor mutations are very subtle, while the effects of other factors can be very large. It is a little like trying to see the ripples produced by a pebble thrown into a stormy sea.

All other variables affecting reproduction, when combined, will significantly interfere with natural selection against any given minor mutation. For example, a high rate of accidental death in a population will override and obscure the subtle effects of minor mutations. Likewise, selection for lethal and near-lethal mutations (which must automatically take precedence) will override the more subtle effects of minor mutations. The fact that most mutations are recessive dramatically masks their negative fitness effects, and

greatly hinders selection against them. Likewise, all interactions between genes ("epistasis") will interfere with selective elimination of minor mutations. In smaller populations, the randomness of sexual recombination (chromosome-segregations and gamete-unions are both random and thus fluctuate) can routinely override selection. These effects cause the fundamental phenomenon of *genetic drift.* Genetic drift has been extensively studied, and it is well known that it can override selection against all but the most severe mutations in small populations. Plant breeders like myself know that *all* extraneous effects on reproduction will interfere with effective selection. The abundance of a single mutation in a population will tend to drift randomly and become immune to selection whenever the net effect of all other factors combined has a greater effect on reproductive probability than does the nucleotide itself.

To put the issue in more familiar terms, selection for very subtle genetic effects is like trying to hear a whisper in a noisy room. Soft whispers, complex messages, and loud background noises will all contribute to the loss of the message. Selection against a minor mutation works best when its fitness effect is still moderately loud, and where there is minimal biological noise. Despite these very significant limitations, selection for a number of minor mutations still works. Thank goodness it works on this level, otherwise we would not be here!

While selection can definitely work for numerous minor mutations, as the **number** of those mutants increases, each mutant's fitness effect becomes less and less significant in terms of total reproductive probability. As the number of minor mutations increases, the individual mutation effects become less and less

significant, and the efficacy of selection for each one moves toward zero. Kimura (1983) alludes to this. I have demonstrated it mathematically in Appendix 2, and the results are shown in Figures 6a-c (pp. 84-86). Each time we add another trait that needs to be selected for, the maximum selective pressure that can be applied to each trait individually must decline. As the number of traits undergoing selection increases, selection efficiency for each trait rapidly approaches zero, and the time to achieve any selective goal approaches infinity. According to my calculations (see Appendix 2), for a population such as our own, the maximal number of mutations which could be selected for simultaneously is approximately 700. Kimura (1983, p.30) alludes to the same problem, and although he does not show his calculations he states that only 138 sites can undergo selection simultaneously, even for a population with very intense total selection pressure (50% elimination) and very weak selective elimination per trait (s = 0.01). Trying to select simultaneously against more than several hundred mutations should clearly lead to cessation of selective progress. Yet even in a small human population, millions of new mutations are arising every generation and must be eliminated! In the big picture, we really need to be selecting against billions, not hundreds, of mutations. Even in the very limited case of selecting for just a few hundred mutations, although it is theoretically possible to do this, it is noteworthy to point out that such highly diluted selection per trait greatly affects the rate of selective progress, which essentially grinds to a standstill. As the number of loci under selection increases, the rate of selective progress (per trait) slows very rapidly, approaching zero. The resulting rate of genetic change would be glacial at best, requiring hundreds of thousands of generations of selection to significantly affect even this very limited number of nucleotide positions.

In a sense, as we select for more minor mutations, each mutation becomes noise for the others. At a distance, a room full of whisperers is full of noise and devoid of net information. As each mutation's effect becomes less and less significant, its individual whisper gets softer, and so the problem of overriding noise gets worse. Even under the best of selection conditions, each individual whispered message cannot be discerned. The effect of any given mutant becomes totally insignificant in light of all other reproductive factors. At this threshold point, the mutation becomes effectively neutral, and all selection abruptly ceases. As we select for more and more minor mutations, we must always reach a threshold point where selection should largely break down. Above a certain number, all minor mutations should become unselectable, even when conditions are ideal and noise is minimal. Simultaneous selection against too many minor mutations should lead to zero selective progress, and genetic drift takes over. In essence, selecting for too many minor mutations simultaneously makes them all behave as *near-neutrals*, as described in the section above.

**Haldane (1957) and Kimura (1983, p. 26) both agree that it is not possible to simultaneously select for a large number of traits due to the cost of selection. This simple reality makes genomic selection virtually impossible.**

**3. Reproductive elimination.** We have learned we cannot stop genomic degeneration because of the high number of mutations occurring in the human population and the prohibitive reproductive cost of eliminating each one. Even more, we have learned we cannot stop genomic degeneration because most mutations are near neutral and their effects are obscured and essentially undetectable above

biological noise. This makes them immune to selection and subject only to drift and degeneration. Furthermore, we have learned that if we try to select against too many minor mutations simultaneously, they effectively all become like near-neutrals. They also become unselectable and subject to random drift. Lastly, I would like to argue that we cannot stop genetic degeneration because we cannot effectively enforce the reproductive elimination of large numbers of mutants simultaneously, for logistical reasons. I have called this problem *selection interference*. This problem has not been addressed sufficiently, but has simply been recognized as a factor interfering with selection (Haldane, 1957; Lynch, Conery, and Burger, 1995; Kondrashov, 1995). When attempting simultaneous selection for tens of thousands–or millions–of different mutants in the genome, the problem of selection interference becomes absolutely overwhelming.

Selection interference occurs when selection for one trait interferes with selection for another trait. For example, a desirable trait will routinely be found along with an undesirable trait within the same individual. To select against the *undesirable* trait automatically means that you are also unintentionally selecting against the associated *desirable* trait (we have to accept or reject the whole person). This association between traits can be very tight (both traits coded for by the very same gene, or two genes side by side on the same chromosome), or the association can be loose (two genes somewhere within an individual). Even if mutations are only loosely associated in the individual, the two traits are still linked for that single generation. Any mutant must always be temporarily linked to thousands of other mutants in every individual and in every generation. Therefore, selection can never operate on a given

mutation in isolation. To select for any given beneficial mutation will always automatically multiply a host of associated deleterious mutations. The problem is inescapable.

To illustrate this, let us imagine selecting between two individuals in a population. Because the genes are drawn from the same "gene pool", any two individuals will have about the same number of mutations and these two sets of mutations will have approximately the same net deleterious effect. When contrasting two such individuals to discover who is more fit, we may find that each has roughly 10,000 different mutations, so there are 20,000 differences between them. Each will have about 10,000 "bad" genic units (mutations) and about 10,000 "good" genic units (non-mutant nucleotides). Due to averaging, the actual difference in genetic fitness between them will be small and will hinge on just a few *major impact* nucleotide differences. Who will actually be reproductively favored? Because of their high degree of overall similarity in genetic fitness, reproductive success will depend more on random chance and noise factors than on true genetic fitness. But even if the "better" individual is favored in reproduction, almost no selective progress will be made. The individual that is favored will have just as many mutations as the rejected individual. We will have *selected away* the 10,000 mutations in one individual, but at the same time we will have *multiplied* another 10,000 mutations in the other individual. Almost all selection is canceled out; 10,000 steps forward and 10,000 steps backward. The only net gain is for those few "major" genes which actually made the real difference in fitness. In higher genomes, selection can only be effective for a limited number of "significant" nucleotide differences. The vast bulk of mutations will be minor or near neutral, will cancel each

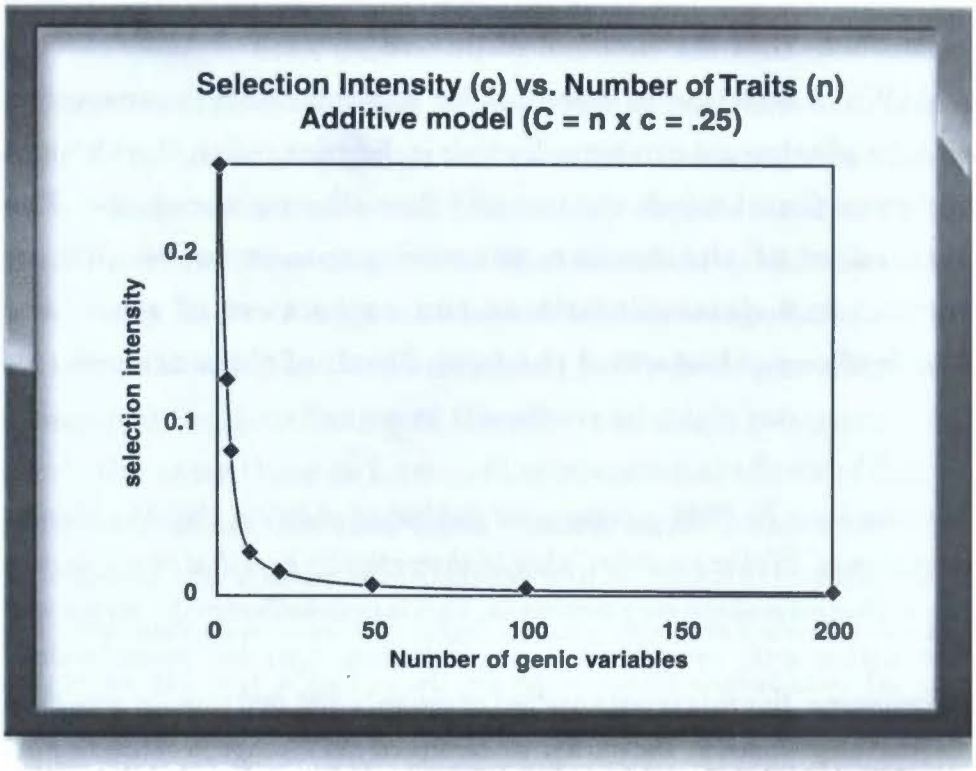
other out, and will be unselectable. On the genomic level, even if we could have perfect control over the reproduction of individuals, we would still fail to effectively prevent the propagation of the vast bulk of deleterious mutations. This problem, to my knowledge, has not been adequately addressed by others, although it is often alluded to by population geneticists.

**4. Selection interference due to physical linkage.** The most obvious and extreme form of selection interference is when there is tight physical linkage between beneficial and deleterious mutations. This results in an irreconcilable problem referred to as "Muller's ratchet". One of the most obvious requirements of natural selection is the ability to separate good and bad mutations. This is not possible when good and bad mutations are physically linked. Essentially all of the genome exists in large linkage blocks (Tishkoff and Verrelli, 2003), so this problem applies to virtually every single building block of the genome. If we refer back to Figure 3d (p. 32), we can see that mutations are overwhelmingly deleterious, but there should be a few extremely rare beneficial mutations. These very rare beneficial mutations might seem to leave a very slight glimmer of hope for forward evolution, but this hope would not be rational because such beneficials will be overwhelmingly nearly neutral (and thus unselectable) and because the accumulating deleterious mutations will always outweigh the beneficials. Yet as long as those rare beneficials are on that graph, they seem to offer a glimmer of hope to the hopeful. The problem of physical linkage erases those beneficials from our graph (Figure 7, p. 87). This should completely eliminate *any* trace of rational hope for forward evolution.

Within any given physical linkage unit, there should be, on average, thousands of deleterious mutations accumulated before the first beneficial mutation would even arise. Therefore, there would never arise at any time even a single linkage group within the whole genome that could realistically experience a net gain of information. Every single beneficial mutation would always be inseparably tied to a large number of deleterious mutations. This can be visualized graphically (Figure 7, p. 87). In Figure 3d (p. 32), we mapped the distribution of the effects of single mutations. We can do the same thing in terms of the mutational effects of linked mutation clusters. Because these clusters never break apart, the net effect of any cluster of mutations will be inherited as if it were a single mutation, and the effect of any mutation cluster would simply be the net affect of all its component mutations. By the time at least two mutations per linkage block have accumulated, nearly every beneficial mutation will have been canceled out by a linked deleterious mutation. At this point, the distribution will already show essentially zero linkage blocks with a net gain of information (see Figure 7). To illustrate this point further, if only one mutation in a million is beneficial, the probability of a linked pair of mutations with both having a net beneficial effect becomes too small to even consider ($10^{-12}$). As more time passes, the average number of mutations per linkage group will increase such that the net loss of information per linkage group will increase, and the complete disappearance of net-gain linkage groups will very rapidly approach *absolute certainty*. The human genome is a composite of roughly 100,000-200,000 linkage blocks. Based upon the logic provided above, we can know with very high certainty that every single one of these "building blocks of evolution" is deteriorating.

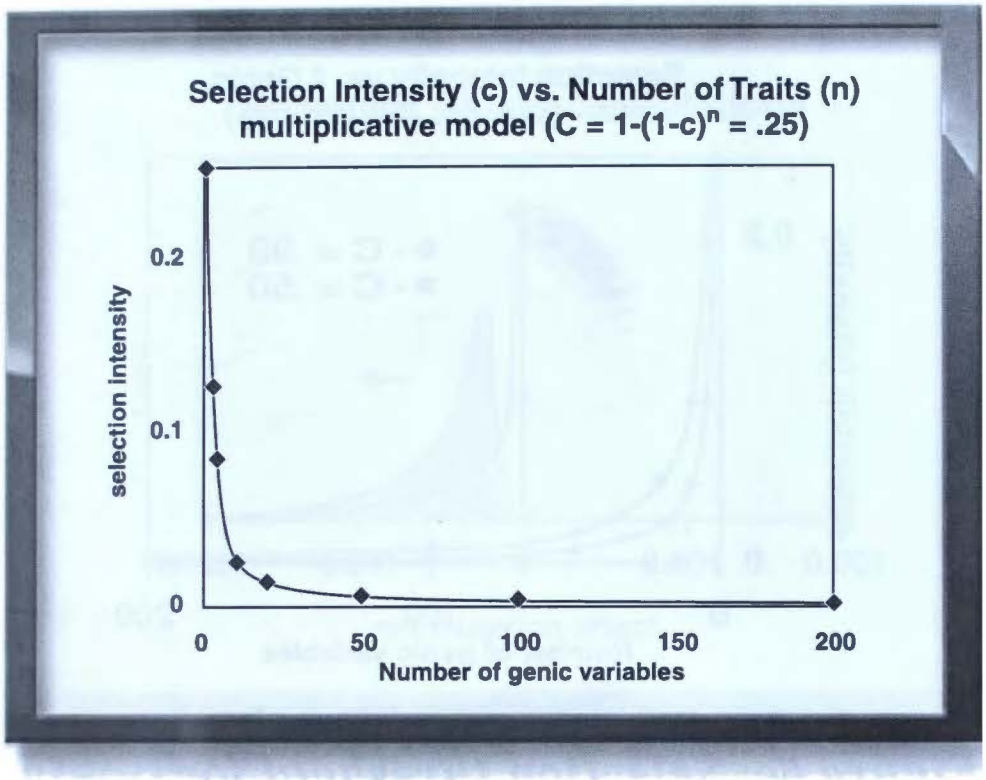
Based upon numerous independent lines of evidence, we are forced to conclude that the problem of human genomic degeneration is real. While selection is essential for slowing down degeneration, no form of selection can actually halt it. I do not relish this thought any more than I relish the thought that all people must die. **The extinction of the human genome appears to be just as certain and deterministic as the extinction of stars, the death of organisms, and the heat death of the universe.**

*Author's note: In 2006 a paper was published showing that the natural operation of "Muller's ratchet" should theoretically be lethal to the human race within an evolutionary time scale. This is especially significant because that author only considered a single linkage unit–the mitochondrial chromosome. But this is only one out of roughly 200,000 linkage groups in the human genome, so the author understated the linkage problem in man by a factor of about 200,000 (Loewe, 2006)!*




## *Figure 6a: Selection Threshold, Additive Model.*

Selection always involves a reproductive cost (C), meaning that some individuals cannot reproduce. Total selection cost must be substantially less than a species' excess reproduction, or the population will rapidly shrink and face extinction. As more traits are under selection (n), the total cost attributable to each trait (c) must diminish rapidly, so that the total cost does not exceed the population reproductive potential. To visualize the problem of selection threshold, I have plotted maximal allowable selection intensity per trait (c) against number of traits under selection (n), for a population which can afford to lose 25% of its individuals for elimination of mutations (C=0.25). As can be seen, the allowable selection pressure per trait plummets extremely rapidly as the number of traits increases. Selection pressures will obviously approach zero very rapidly and a threshold point will be reached where each trait is effectively neutral. This curve is based on an additive model, following the formula C = n x c (see Appendix 2).




## *Figure 6b: Selection Threshold, Multiplicative Model.*

The additive model illustrated in Figure 6a can be contrasted with the multiplicative model shown here. The curve above follows the formula $C = 1 - (1-c)^n$ (see Appendix 2). The two curves in 6a and 6b are essentially identical. In both cases, the maximum allowable selection pressures rapidly approach zero as number of traits under selection increases. In both cases, a threshold point will rapidly be reached where each trait is effectively neutral.

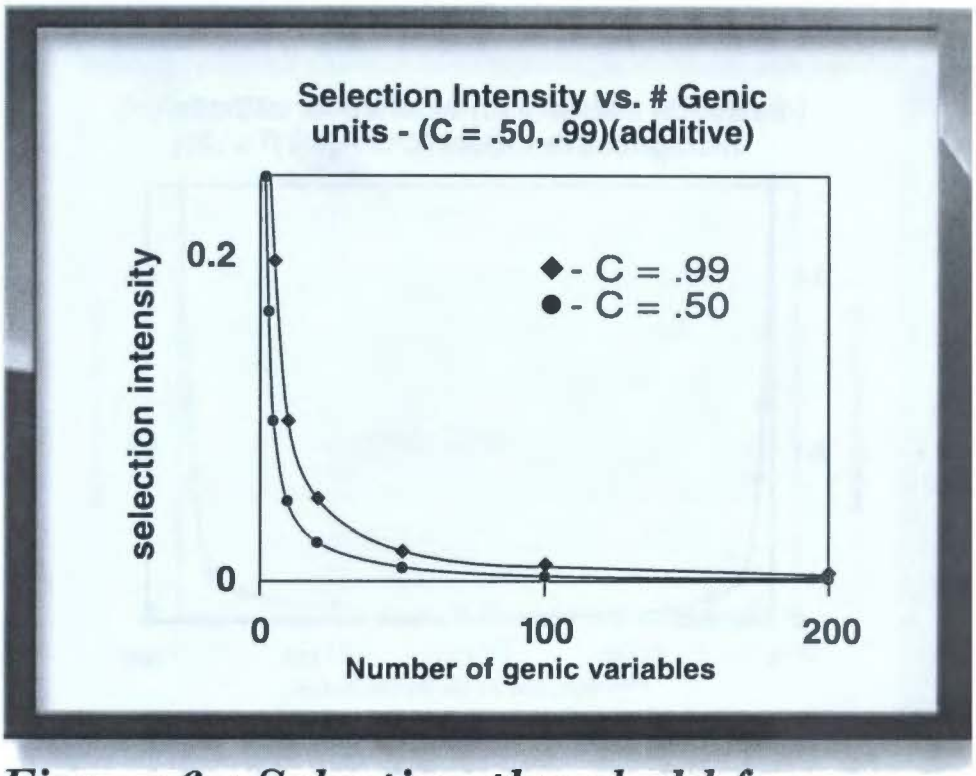
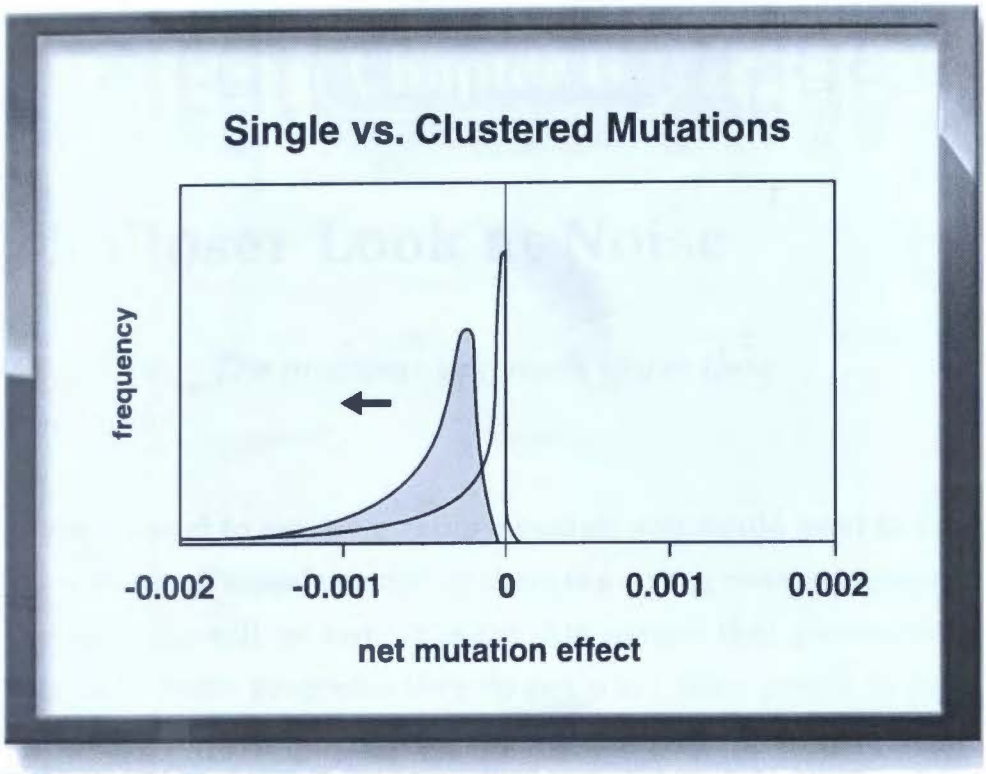



***Figure 6c: Selection threshold for extremely fertile populations.***

Doubling human fertility, up to very unrealistic levels (C=0.5), does not significantly reduce the problem shown in Figure 6a. Even for extremely fertile species, such as plants, where C may be 0.99 (100 offspring per plant), the problem of selection threshold is still very real. Selecting for many traits simultaneously decreases selection efficiency for each individual trait, until selection reaches a point where it is entirely ineffective. These curves follow the additive formula: $C = n \times c$.




## *Figure 7.*

Mutation clusters will always be 100% deleterious. In Figure 3d (p. 32), we saw that the distribution of individual mutations is skewed toward neutral, and that while there are many deleterious mutations, there are vanishingly few beneficial mutations. These rare beneficial units disappear when we analyze mutations as they actually occur within physically linked clusters. The actual distribution of the effects of linked mutation clusters (the shaded distribution curve), will be strongly shifted to the left when compared to individual mutations. Any linked mutation cluster will be inherited as a single genetic unit and the effect of that mutation cluster will simply be the net effect of all of its component mutations. The fitness effect of any cluster can be calculated to be the *average effect of its individual mutations times the number of mutations within that cluster*. Any rare beneficial will be quickly cancelled out with high certainty. Since the vast majority of mutations are deleterious, each mutation cluster will have an increasingly negative affect on fitness each generation. By the time there are just two mutations per linkage group, nearly all beneficial mutations will have been cancelled out by at least one linked deleterious mutation. As the mutations accumulate beyond two mutations per cluster, it becomes increasingly certain that there will be no linked cluster left with a net beneficial effect.

Chapter 6

# A Closer Look at Noise

*Newsflash – The problems are much worse than you think!*

If you wanted to receive a radio message, you would need to limit the amount of "noise" or static. If there is a strong interfering signal, the message will be lost. It is for this reason that governments can "jam" radio programs they do not want their people to hear. Likewise, if governments do not regulate the allowable bandwidth for each radio station, stations very soon become noise *for each other*. Radio static can arise from many sources: other radio stations, solar flares, cosmic radiation, radio waves being reflected by cloud cover, electric motors running in the neighborhood, local walkie-talkies, etc. Regardless of the source, noise results in loss of information.

A very weak signal is easily destroyed by any amount of noise. The weaker the signal and the greater the noise, the more certain is that loss of information. A low signal-to-noise ratio always ensures loss of information. When we receive a signal plus noise, *amplification* does not help us. Turning up the volume on your radio does not help overcome static. We just wind up amplifying the static as much as the signal. To ensure minimal loss of information, there must be a favorable signal-to-noise ratio.

The reason that most nucleotides must be unselectable is because of consistently low signal-to-noise ratios. Likewise, the reason we cannot select for many nucleotides simultaneously is because of rapidly shrinking signal-to-noise ratios. In fact, one of the primary reasons selection cannot save the genome is because of ubiquitous noise. When we apply selection to the entire genome, the signal-to-noise ratio quickly approaches zero. Hence, noise will consistently outweigh the effects of individual nucleotides in the big picture. This is a primary reason why selection works on the level of the gene, but fails on the level of the genome.

In genetics, the signal-to-noise ratio is often expressed in terms of "heritability". Heritability is the important difference between genotype and phenotype. If a trait has high heritability, most of the variation observed for that trait is genetically heritable, and it will be easy to select for. The essence of this concept of heritability is simply the ratio of heritable versus non-heritable variation. Non-heritable variation is largely due to variation within an organism's individual environment, and is the source of phenotypic noise. So a genetic heritability value for a trait is essentially equivalent to a signal-to-noise ratio. For example, any observed difference in the intelligence of two people will be partly due to heritable genetic differences (genic differences which can be passed from parent to child), and partly due to environment (i.e., nutrition, the quality of training, etc.). So intelligence is determined partly by *nature* (inherited capabilities), and partly by *nurture* (non-inherited characteristics). This is equally true for height, speed, weight, etc. In a sense, heritability can be understood as a reflection of the ratio of nature to nurture. When heritability is "1" for a trait, that trait is 100% hereditary (i.e., blood type), and it is not affected

by environment at all. If heritability is "0" for a trait, that trait is not inherited; it is entirely environmental in nature (e.g., a tattoo). A simple trait such as height is usually quite highly heritable ($h^2 = 0.3$). This specifically means that for such a trait, 30% of the phenotypic variation is heritable (selectable) variation. Unfortunately, for very complex traits such as fitness, heritability values are low (even as low as 0.004), and can approach zero (Kimura, 1983, pp. 30-31). This is because *total fitness* combines all the different types of *noise* from all the different aspects of the individual.

When Kimura says that fitness heritability is generally very low, he means that almost all variation for individual fitness is due to non-heritable (non-selectable) effects. Thus, almost all selection for fitness will be *wasted.* **Low heritability means that selecting away bad *phenotypes* does very little to actually eliminate bad *genotypes.*** Consider seeds falling off a tree. Some seeds will land on fertile ground ideal for growth. But most seeds will land on places that are too dry, too wet, too many weeds, too much shade, too many people, etc. The result will be great diversity in the health and vigor of the resulting trees, and huge differences in their survival and reproduction. But almost all of this "natural selection for the fittest" will really only be selection for the *luckiest*, not the genetically superior. Hence, in most natural situations, most phenotypic variation in fitness will only be due to non-genetic noise, and will have very little to do with heritable differences. This is what we mean by low heritability. Low heritability largely neutralizes the effectiveness of selection. Like an automobile with a racing motor but a broken transmission, there can be lots of selection happening, yet almost no genetic progress.

Let us further consider what is involved in non-heritable variation for fitness by referring to Figure 8a (p. 100). Obviously, variation in environment can create major differences between individual phenotypes. It is often estimated that about 50% of all phenotypic variation is due to just environmental variation. If one plant is growing better than another plant in the same field, there is a high probability it is growing better just because it sits on a slightly more favorable piece of soil. This aspect of phenotypic variation is shown in sector 1 in Figure 8a. This type of variation strongly interferes with effective selection by adding to non-heritable noise and diminishing the signal-to-noise ratio.

The second largest part of phenotypic variation is called "environment-by-genotype" interaction. This is often estimated to represent about 25% of all phenotypic variation. Given two plants in the field, if we change the environment by irrigating the field, the extra water may be good for one plant but bad for the other, depending on their genotype. This type of variation is not consistently heritable. Like environmental variation, this aspect of phenotypic variation adds to the noise and interferes with selection. This is shown as sector 2 in our pie-chart.

The third largest part of phenotypic variation is non-heritable genetic variation. That may sound like a contradiction, but it is not. A large part of genetic variation is due to factors that are not passed down consistently from generation to generation. These factors include epigenetic effects (sector 3), epistatic effects (4), dominance effects (5), and genetic effects subject to cyclic selection (6). To make a long story short, most genetic variation is not heritable, at least not in a linear and selectable manner.

The only fraction of genetic variation that is heritable (and therefore potentially selectable) is what is called additive genetic variation (sector 7). Very simply, additive genetic variation is where a given trait (or nucleotide) is unambiguously and consistently better than an alternative trait (nucleotide) within the population. For a complex trait such as fitness, this type of additive genetic variation makes up a very small part of the total phenotypic variation. If Kimura is correct that fitness heritability can be as low as 0.004, then as little as 0.4% of such phenotypic variation would be selectable. This represents a signal-to-noise ratio of about 1:250. One way of expressing this is that 99.6% of phenotypic selection for fitness will be entirely *wasted.* This explains why simple selection for total phenotypic fitness can result in almost no genetic gain.

If we have a trait, such as fitness, which has low heritability (Figure 8a), and we have a species of low fertility such as man (Figure 8b, p. 102), we can see that only a tiny part of a population can be used for effective selection (Figure 8c, p. 103). If we can only selectively eliminate about 16.7% of a population, and only 0.4% of that selection is actually effective, then only 0.07% of that population can be employed for truly *effective* selective elimination. In other words, less than 1 person in 1,000 is available for the *effective* elimination of all deleterious mutations, and for the *effective* fixation of any possible beneficial mutations.

The heritability for a single *trait* such as total fitness can be remarkably small, yet the heritability of a typical *nucleotide* is infinitesimally smaller. Let us consider the heritability of an average single nucleotide mutation, an unorthodox but useful application of the concept of heritability. The "signal" (i.e., the

heritable additive fitness value of such a nucleotide) is inherently too small to measure. But the "noise" is astronomical. It is the combined effect of all the non-heritable components of variation plus the effects of all the other segregating nucleotide positions! In a typical population there are millions of other segregating nucleotides. So the effect of an average single nucleotide will very consistently be lost in an *ocean of noise*, with signal-to-noise ratios consistently less than one to one million. The heritability of such a nucleotide is not significantly different from zero, explaining why most nucleotides are inherently unselectable and must be termed nearly neutral by Kimura's definition.

**Another major source of noise is probability selection, not threshold selection.** As a plant breeder I would score hundreds of plants for their phenotype (yield, vigor, disease resistance, etc.), and then I would rank them from best to worst. I would decide what fraction of the population I wished to eliminate, drawing a line through the ranking at the desired level and keep only those plants above the mark. This is called "truncation selection" and is used by breeders because it is especially effective. However, this type of selection never happens in nature. Natural selection is always based only upon probability. Mother Nature does not tabulate for each member of a population some fictional "total fitness value" based upon total phenotypic performance for all traits combined. Mother Nature does not then rank all the individuals. Lastly, Mother Nature does not draw an arbitrary line and eliminate all individuals below that line. Instead, the phenotypically inferior individuals simply have a slightly lower probability of reproduction than the others. Very often, by chance, the inferior individual will reproduce, and the superior individual

will not. In fact, there is only some modest correlation coefficient that relates phenotypic superiority with reproductive success. The more reproductive noise (i.e., random survival/mating), the weaker the correlation becomes, and the less certain it becomes that a superior individual will actually be favored in reproduction. If we realistically disqualify all types of truncation selection from the evolutionary model, the result is the addition of a whole new level of noise, which further reduces the effectiveness of selection.

The nature of the non-truncation problem is easy to illustrate. Picture a population of shrimp swimming en masse, and a whale comes and swallows half the population in one bite. Is this an example of survival of the fittest among the shrimp? Was there a precise ranking of most fit to least fit, followed by a strict cut-off type of selection? Alternatively, picture a large mass of frog eggs in a river. A large number of eggs are eaten by fish, even before they hatch. A large number of tadpoles are picked off by birds, a boat is launched and squishes a few hundred more, many more are swept over a waterfall. Many maturing adults burrow into a mud bank which is later removed by a dredging operation, and most of the surviving adults are picked off by more predators. Almost all the elimination has been random. Once again, we are seeing survival of the *luckiest*. So where is the systematic sorting by phenotype? It is largely absent! There is a huge element of noise, not just in determining who has the best phenotype, but also in terms of differential survival and reproduction. Noise affects reproductive success *in spite of phenotype* and this noise is *over and above* the noise we have considered in the heritability section above. Therefore we should never model truncation selection in any honest natural selection scenario. Furthermore, we must honestly use a relatively

low correlation coefficient when calculating the probability that a superior phenotype will reproduce. Perhaps 50% of reproductive failure is independent of phenotype (Figure 8b, p. 102).

**There is a third level of genetic noise called gametic sampling.** This is the statistical variation associated with small population sizes. If you toss a coin many times, you will predictably get about 50% heads and 50% tails. However, if you toss the coin just 10 times, there is a good chance you will *not* get 50/50. The frequency of each possible outcome is readily predicted by using probability charts. This same type of statistical variation occurs when a gene or nucleotide is segregating within a population. Gene segregations tend to be highly predictable in very large populations, but they will fluctuate very significantly in smaller populations, just like the outcomes of a series of coin tosses. Such statistical fluctuations result in what is called genetic drift. This means gene frequencies can change regardless of the presence or absence of selection. This simple probability element of fluctuating gene frequencies is well studied.

Classically, population geneticists have dealt with genetic noise only on the level of this last type of noise, gametic sampling (probability fluctuations), which is very sensitive to population size. Random genetic drift is very strong and can override the effects of even substantial mutations in small populations. This is why the populations of endangered species are especially subject to what is called *mutational meltdown*. In small populations, natural selection is largely suspended. It is on the basis of gametic sampling that Kimura first defined his near-neutral mutations. It is for this same reason that Kimura calculated the size of his no-selection

box (Figure 3d, p. 32) as a simple function of population size (either plus or minus $1/2N_e$). It is very attractive for the genetic theorist to limit consideration of noise to just gametic sampling. This is because one can conveniently make noise from gamete sampling largely disappear simply by imagining larger populations. At the same time the theorist can make selection itself periodically "go away" by invoking high-noise episodes associated with small population *bottlenecks* (e.g., the Out-of-Africa theory).

Gametic sampling is only a minor part of total genetic noise, and the other two important aspects of genetic noise *are only partially diminished in large populations*. We cannot make noise "go away" by invoking larger population sizes. Noise is *always* present, and at much higher levels than is normally acknowledged by population geneticists. In fact, very large populations invariably have *enhanced* noise. This is due in part to population substructure (many smaller sub-populations, each with its own gametic sampling fluctuations). It is also because larger populations extend over a wider range of environments, becoming subject to even more environmental variation. Large population size does not reduce the random elements of reproduction, nor does it reduce the phenotypic masking of genotype. Noise **always** remains a severe constraint to natural selection. Under artificial conditions, plant and animal breeders have been able to very successfully select for a limited number of traits. They have done this by employing intelligent design to deliberately minimize noise. They have used blocking techniques, replication, statistical analysis, truncation selection, and highly controlled environments. Natural selection does none of this. It is, by definition, a blind and uncontrolled process, subject to unconstrained noise and unlimited random fluctuations.

**What are the genetic consequences of all this noise?** When we realize that high levels of genetic noise are unavoidable, we realize we cannot wave away the no-selection box in Figure 3d (p. 32), not even by invoking larger population sizes. As we come to appreciate that there are two entire levels of noise above and beyond gametic sampling, we realize the box must be corrected (see Figure 9, p. 104). Kimura's no-selection box must be expanded significantly, based on the imperfect correlation between genotype and phenotype, and based upon the imperfect correlation between phenotype and reproductive success. The result of these two imperfect correlations is that the number of near-neutral (unselectable) nucleotide positions is greater than commonly realized, and their abundance is not strictly dependent on population size. Small population size certainly aggravates the noise problem, but large population size cannot eliminate this problem (for more detailed discussion see Appendix 5).

The pervasive existence of serious genetic noise amplifies virtually all my previous arguments regarding the limits of selection. Kimura's no-selection box gets bigger (Figure 9) because huge numbers of otherwise minor mutations become nearly neutral and unselectable. The selection threshold problem, wherein simultaneous selection for too many traits results in a complete cessation of progress, will happen much sooner because of high levels of noise. Lastly, the noise problem will result in most "selection dollars" being completely wasted (Figures 8a-c, pp. 100-3). This greatly increases the actual cost of selection, and severely increases the very real limits that "cost" places upon any selection scenario.

To get a more intuitive understanding of the noise problem, we can return to some of our visual analogies. In terms of our evolving red wagon, try to imagine a situation where wagon performance was influenced much more by *workman errors* on the assembly line than by the *typographical errors in the assembly manual.* Can you see that the quality control agent would mostly be wasting his time and resources by selecting for "non-heritable" variations? In terms of our Princess, the noise problem is like having innumerable pea-sized lumps within her mattresses. Wouldn't that make her problem worse? In terms of our biochemistry textbook, the noise problem is like having most of the typos in the textbook fail to be passed on into the next printing cycle. This would further reduce the already vanishingly small correlation between typographical errors and student scores. In all these examples, when we add any reasonable level of noise, these already absurd scenarios just become even more impossible!

The late Stephen Jay Gould, like Kimura, argued against the strict selectionist view of evolution. In terms of the survival of entire species, he recognized the importance of natural disasters, "survival of the luckiest", and noise. **What Gould and Kimura both seem to have failed to realize is that if noise routinely overrides selection, long-term evolution is impossible and guarantees genetic degeneration and eventual extinction.**

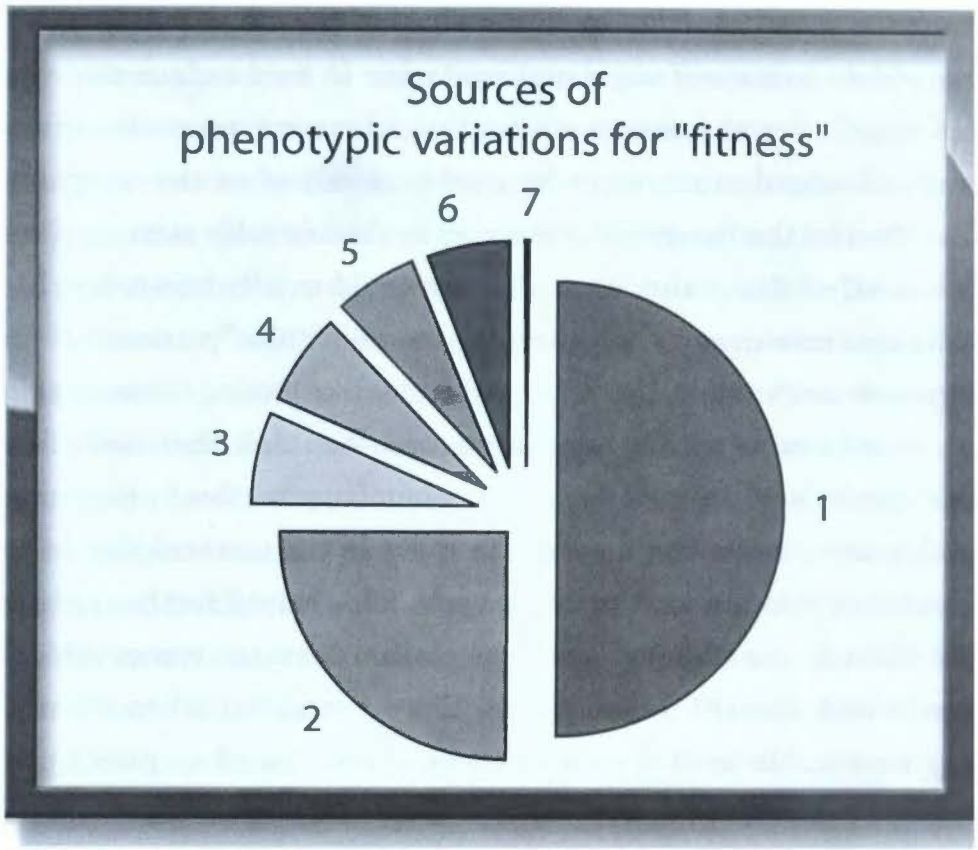
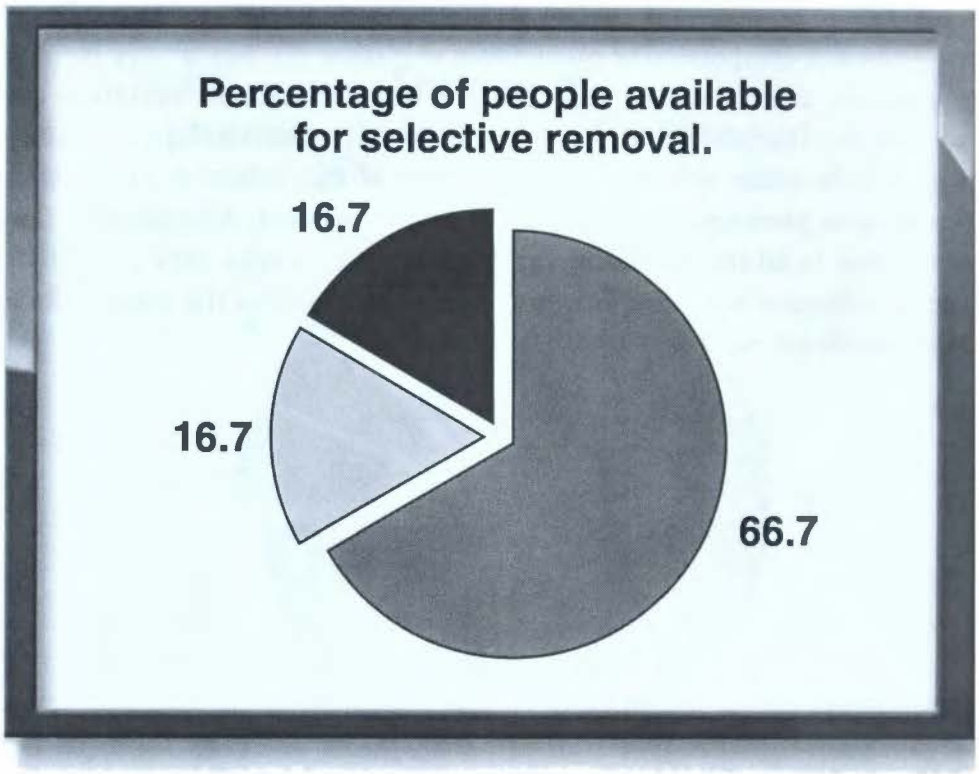



***Figure 8a: Sources of phenotypic variation.***

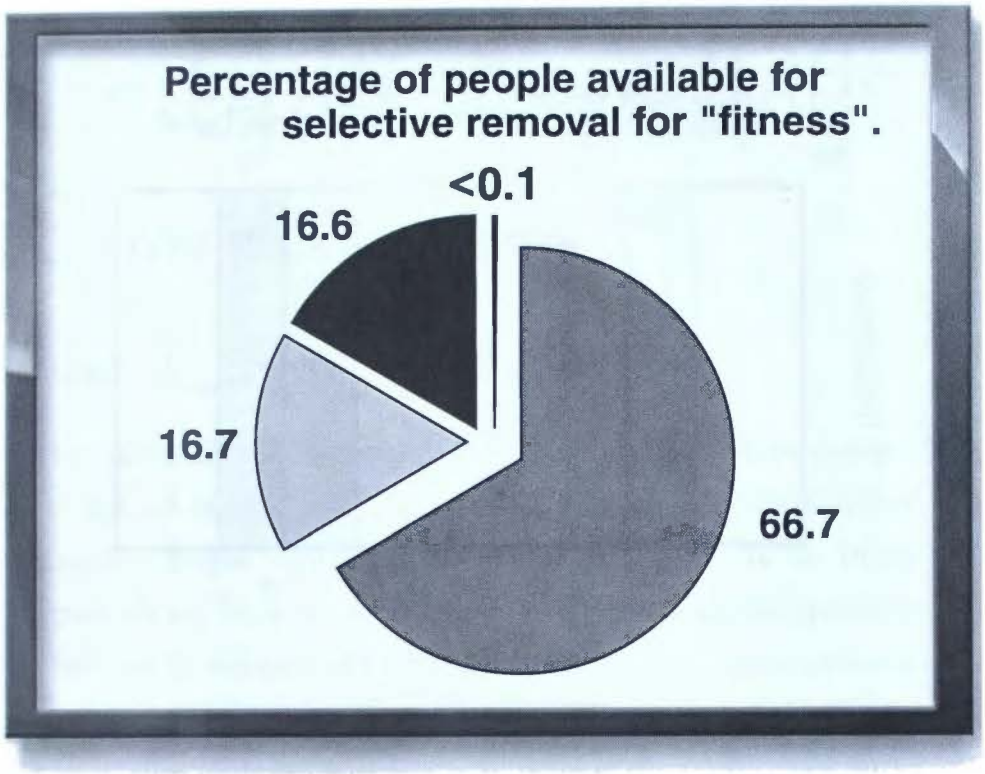
Variation between individuals comes from numerous genetic and non-genetic factors. Within the genetic component of phenotypic variation, there are also numerous components. Only one genetic component is "selectable" and that is the "additive" genetic component. But this component is totally overshadowed by the other sources of phenotypic variation. The primary source of phenotypic variation is environmental variation (sector 1). This variation is not heritable and interferes with selection. The second major source of variation is the interaction of the environment with the genotype (2). This variation is also not heritable and interferes with selection. Within the genetic component of variation, there is variation due to: epigenetics (3), epistasis (4), and dominance (5). None of these genetic components are heritable and all of them interfere with true long-term selection. Lastly, there are other genetic components which would otherwise be selectable but are "neutralized", either by homeostatic processes or such things as cyclic selection (6). All these non-heritable components account for the vast bulk of all

phenotypic variation. This leaves additive genetic variation as a relatively insignificant component of phenotypic variation (7). For a very general phenotypic trait, such as reproductive fitness, additive variation can account for less than 1% of total phenotypic variation (Kimura, 1983, p.30-31). In other words, more than 99% of any selective elimination based upon phenotypic superiority is *entirely wasted.* All variation that is not due to additive genetic variation actually works very powerfully *against* effective selection! It acts as noise and obscures the actual effects of heritable genetic variations.



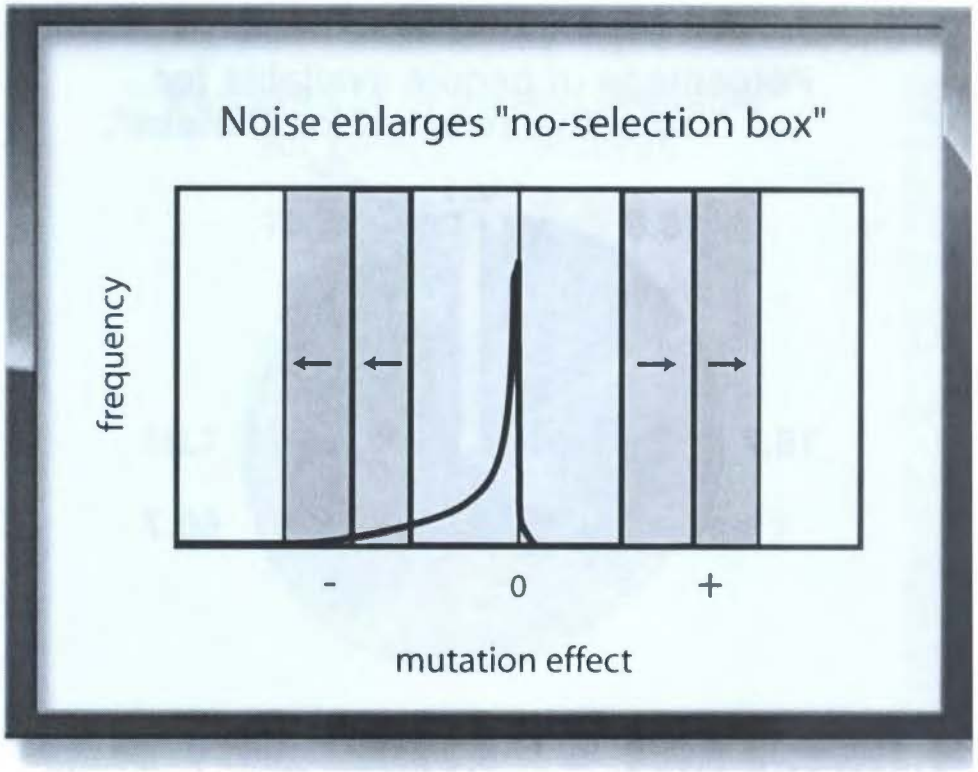

## *Figure 8b.*

Only a limited proportion of any population (the *population surplus*) can be selectively eliminated. Given the current global rate of human reproduction (three children per couple), two-thirds of all children must reproduce for simple replacement. This maximally leaves one-third of the children available for selective reproductive elimination. However, a significant fraction (perhaps half) of the population's surplus will fail to reproduce for entirely random causes such as war, accidents, and choice, which have nothing to do with phenotype. So only about one-sixth (16.7%) of the human population is actually available for any potential selective elimination. This is in keeping with Haldane's estimate that only about 10% of a human population is actually available for selection.




## *Figure 8c.*

Selective elimination within human populations based on phenotypic fitness (a very general trait) has an effectiveness approaching zero. This is seen when we combine Figures 8a and 8b. Of the 16.7% of the human population theoretically available for selective removal based upon phenotypic inferiority, as little as 0.4% of such removal will result in any heritable effect on succeeding generations. This means less than 0.1% (16.7% x 0.4% = 0.07%) of the total population would be available for effective selection. This is too small a fraction to show accurately in this type of graph. In a sense, this means that less than one person in a thousand can be removed for truly *effective, selective, reproductive elimination.* Even if someone like Hitler were to "kill off" as many phenotypically "inferior" human beings as possible every generation, it would result in insignificant selective progress for something as general as "fitness". This conclusion is a logical extension of low human fertility rates and the extremely poor heritability of a trait as complex as fitness (Kimura, 1983, p.30-31).




## *Figure 9.*

Kimura's no-selection box, as shown in Figure 3d (p. 32), is based upon a minimal estimate of noise (i.e., only that attributable to gamete sampling). This is the classic near-neutral model, but this view fails to recognize all sources of noise. So Kimura's classic no-selection box is too small. We need to first expand our no-selection box because of poor heritability, which arises from the imperfect correlation between genotype and phenotype (more than 99% of phenotypic variation can be non-heritable [Figure 8a]). We then need to expand our no-selection box further in order to account for the imperfect correlation between phenotype superiority and reproductive success that arises from the random aspects of reproduction (Figure 8b). These are the primary sources of noise. When we consider **all** sources of noise, we realize that the real "no-selection box" is large, and that it cannot be dismissed by simply invoking large population sizes.

# Chapter 7

# Crow to the Rescue?

*Newsflash – Crow solution fails reality test.*

Is the net information within the genome going up or going down? We can, at best, wave our hands when we speculate about how selection might synthesize *new* information. It is inherently hypothetical. In a sense it becomes a philosophical question and is not really subject of scientific analysis. Strong arguments can be made against mutation/selection creating new information, but theorists can always speculate to the contrary (it is very difficult to prove something can never happen). However, I believe the "going down" aspect of the genome is subject to actual scientific analysis. It is for this reason that I have focused on the issue of the degradation of information. I believe it is subject to concrete analysis. Such analysis persuasively argues that *net* information must be declining. If this is true, then even if it could be shown that there were specific cases where new information *might* be synthesized via mutation/selection, it would still be meaningless since such new information would promptly then begin to degenerate again. The net direction would still be *down*, and complex genomes could never have arisen spontaneously.

If the genome is actually degenerating, it is bad news for the long-term future of the human race. It is also bad news for evolutionary theory. If mutation/selection cannot *preserve* the information

already within the genome, it is difficult to imagine how it could have *created* all that information in the first place! We cannot rationally speak of genome-building when there is a net loss of information every generation! Halting degeneration is just a small prerequisite step before the much more difficult question of *information-building* can reasonably be opened for discussion (see Chapter 9).

In the last decade, concern about the mutation rate has been growing among geneticists as it has become more and more clear that the rate of deleterious mutations must be much higher than one per person per generation (Neel et al., 1986). One way for theorists to dismiss this problem has been to claim that most DNA is actually *non-information*, hence most mutations are perfectly neutral in effect. By this logic, if the actual rate of nucleotide substitution was 10 per person, then by defining 98% of the genome as junk DNA, the *effective* mutation rate must be only 0.2 per person. So the number commonly quoted in the media and textbooks would then be 0.2, not 10. However, as the known rate of mutation has been increasing, and as the recognized percent of functional DNA has been increasing, even this rationale has failed to explain away the problem of genetic degeneration. At this point, a distinguished geneticist, Dr. James Crow, described a model of natural selection which seemed to save the day (Crow, 1997).

Dr. Crow acknowledged that in any population when the rate of deleterious mutations approaches 1 per individual, such mutations must begin to accumulate and population fitness must decline. However, as the total number of accumulated mutations per person becomes quite large, he realized that some individuals would

have significantly more mutations than others (due to chance). He proposed that by focusing selection against such individuals, one could sweep away a disproportionate number of mutations. The consequence would be that more mutations in the population would be eliminated at less "cost" to the population. Eventually, the number of mutants per person might then be stabilized, and the decline in fitness would taper off. This model seems to work in simple mathematical simulations, when it is assumed that all mutations are extremely minor, and all have an identical effect. An eventual leveling off of mutation accumulation is shown in the typical computer simulation summarized in Figure 10a (p. 112). Assuming artificial truncation selection based solely upon mutation count per individual, mutations accumulate to high numbers, but their increase eventually starts to taper off. However, the nature of this curve is surprising in that it still shows a disastrous accumulation of mutations. It is very informative to look at how the same simulation affects fitness. In Figure 10b (p. 113), we see what happens to fitness over time, even when we assign to each mutation the tiniest reasonable average value for mutation-effect (0.0001). If we lower this value much more, we would be in the near-neutral range, which would make all such mutants entirely unselectable. What we see is that average fitness of the individuals in the population plummets essentially to zero (the species goes extinct) in just 300 generations. What type of evolutionary scenario is this? This model involves extreme back bending, yet it still fails to stop catastrophic genomic degeneration. Moreover, the question remains, "Does this highly artificial mathematical model match in any way what is really happening in nature?"

As mentioned earlier, we are all highly mutant, so selection must be between "more mutant" versus "less mutant" individuals. There are two of ways deciding. The first, of minor importance, is the question, "Who has the most mutations?" The second, of primary importance, is the question, "Who has the worst mutations?" The model described by Crow only considers the former, while ignoring the latter. The Crow model is an imaginary construct evidently designed to obscure a major theoretical problem.

Because each of us is made up of genes that represent a more or less random sampling of the human "gene pool", we should each have very nearly the same total number of accumulated mutations per person. The actual difference in total number of mutations between two people will be quite trivial, only representing sampling variation (i.e., minor variations from the population's average). We know this because these mutations have been accumulating and mixing within the "gene pool" for many generations. Such mutations have grown very abundant, and mutation count should be quite homogeneous. Thus "mutation count" will be a very minor variable in terms of differences between individuals.

If our genes are just samples from a large and well blended "gene pool", why are we, as individuals, so distinct from one another? The answer to this question lies in the fact that nucleotide differences have very different degrees of impact, ranging from lethal to neutral. True lethals reduce fitness 100% (zero reproduction). Typical minor mutations might reduce fitness by only 1 or 2%. Many near-neutrals will only reduce fitness by a millionth of a percent or less. Because of all this, the fitness impact of different nucleotides can vary by *many orders of magnitude*. This means

that the very striking genetic differences we see between human beings are not due to their total number of mutations. Rather, most obvious variations are due to the specific effects of a relatively few high-impact genic differences. Just one minor mutation can overshadow the effects of a *million* near-neutral mutations. One person may have several thousand fewer mutations than another, yet just one specific mutation can still make that person much less fit. Therefore, the idea of counting the total number of mutations per individual, and then selecting away high-count individuals is not a reasonable mechanism to get rid of mutations. This concept appears to have been invented as a mathematical trick to attempt to rationalize how to get rid of more mutations, using less selection cost. Although this process may be operating to a very limited extent in nature, it is very clearly *not* what is generally happening.

Overwhelmingly, fitness variation between members of a population should be due to a few specific and high impact genetic variations, and not to the total mutation count per person. A limited number of relatively major nucleotide variants are the real basis for the obvious differences we see between individuals and between races. Therefore, the limited number of "significant" nucleotides must be the real basis for all adaptive natural selection, and must also be the real basis for all artificial breeding of plants and animals. Even while selection can progress rapidly for a handful of variants at *major nucleotide sites*, the genome must still be degenerating *as a whole*, for all the reasons we have been discussing. Any appearance of genetic improvement is superficial. Your car is still rusting away, even if you get a new coat of paint. The movie star is still aging, even if she gets a new facelift.

In dealing with the concepts above, one will encounter the term "synergistic epistasis". When I first encountered this phrase I was very impressed. In fact, I was intimidated. It seemed to speak of a very deep understanding–a deep knowledge I did not possess. As I have seen it used more, and have understood these issues better, I believe I have come to understand the term better. It is a sophisticated expression but signifies nothing. It has all the appearance of deliberate *obfuscation*. Literally translated, synergistic epistasis means "interactive interaction". Does that help us? Fancy terminology is often used to hide lack of understanding. "Punctuated equilibrium" is an excellent example of a phrase that sounds impressive but explains little. To the extent we can attribute any meaning to the term synergistic epistasis, it means that mutations interact such that several mutations cause more damage collectively than would be predicted by their individual effects. At least one paper provides experimental evidence that the concept is not valid (Elena and Lenski, 1997). But even if it were valid, it makes the genetic situation worse, not better. We have *always* known that genic units interact, and we know that such *epistasis* is a huge impediment to effective selection. This fact is ignored by most geneticists because selection scenarios become hopelessly complex and unworkable unless such interactions are conveniently set aside. But now, when genetic interactions can be used to cloud the problem of error catastrophe, the concept is conveniently brought forth and used in an extremely *diffuse and vague* manner, like a smoke screen. But let's look through the smoke. If multiple mutations really *do* create damage in a non-linear and escalating manner, then error catastrophe would happen much sooner and populations would spiral out of control and into mutational meltdown much faster. We would already

be extinct! Once again we are looking at a conceptual "sleight of hand", which clearly does not apply to the real world, and which is only aimed at propping up the Primary Axiom.

Before leaving the subject of the Crow model, it should be pointed out that Crow's argument only addresses the problem of *cost of selection*. So even if Crow's model could be shown to be sufficient and fully operational in nature, the human genome should still deteriorate because of the many other reasons I have described, including the problems of near-neutral mutations, selection threshold for too many minor mutations, and selection interference.

**By now we should clearly see that the Primary Axiom is not "inherently true", nor is it "obvious" to all reasonable parties, and so it is very clear that it should be rejected as an axiom. Moreover, what is left, the "Primary Hypothesis" (mutation/selection can create and maintain genomes), is actually found to be without any support! In fact, multiple lines of evidence indicate that the "Primary Hypothesis" is clearly false and must be rejected.**

*Author's note: Biologically realistic numerical stimulations (see Sanford et al., 2007a; 2007b), have now been used to show that neither the "Crow mechanism" nor "synergistic epistasis" can stop mutation accumulation.*

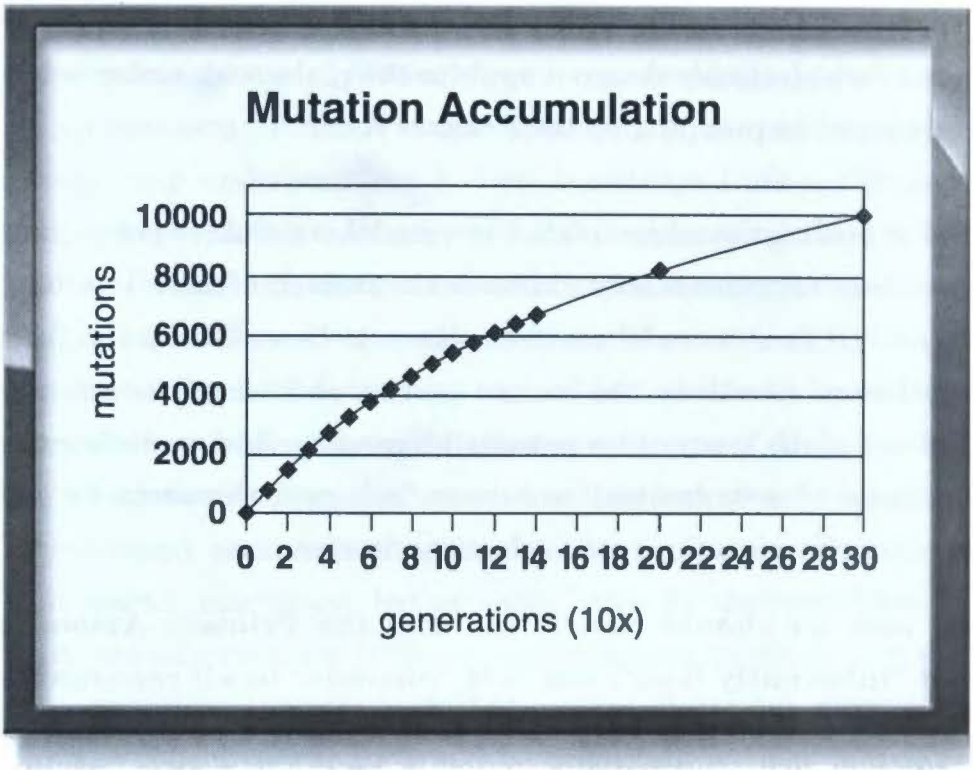



***Figure 10a: Crow's mutations.***

At my request, Walter ReMine has kindly developed software to perform numerical simulations of Dr. Crow's model of truncation selection based on mutation count. This curve plots the average number of mutations accumulated per person after (n) generations, assuming sexual recombination, 100 individuals in the population, 100 mutations per person, 4 offspring per female, 25% non-genetic (random) elimination, and 50% selective elimination of the remainder per generation. Although the rate of mutation accumulation eventually begins to level off, this does not happen until very serious genetic damage has been done, and there is no reason to expect this to occur given a more realistic model. Crow's model is designed to make the problem of mutation accumulation "go away". It assumes that all mutations have equal value, that all are individually very subtle (but not "nearly neutral"), that selection is based upon mutation count, and that artificial truncation selection is operational. None of these assumptions are remotely reasonable. Even though all these assumptions are artificial, the numerical simulation still shows severe mutation accumulation. Almost identical mutation accumulation curves have been modeled by Schoen et al., 1998.

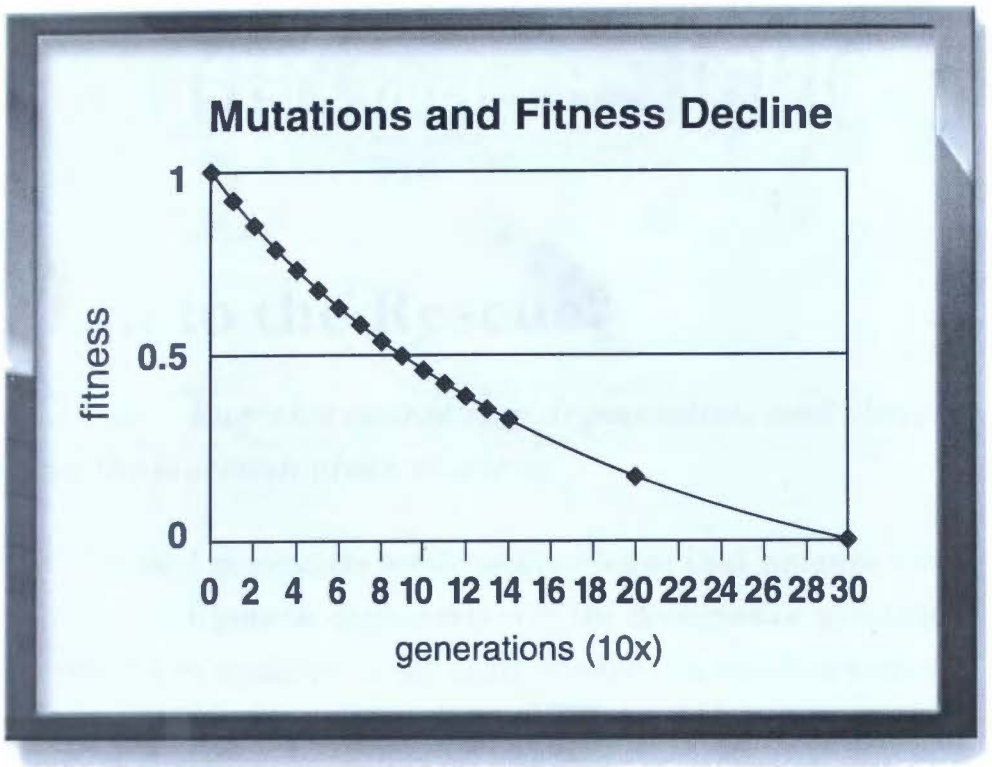



***Figure 10b: Crow's fitness decline.***

Using the data shown in Figure 10a, we can plot average population fitness over time, assuming Crow's model of truncation selection based on mutation count. We must assign an average value to the mutations that are accumulating. We can assume the average mutation value is at least 0.0001 (each mutation reduces fitness only one part in ten thousand). This level of average mutation effect is very conservative. As seen above, as mutations accumulate, the average fitness naturally declines. Assuming an additive model, the result is that our species goes extinct in roughly 300 generations. Yet if we reduce the average mutation effect to substantially less than 0.0001, we would arguably be making all the mutations effectively neutral, and therefore unselectable. If the average mutation actually becomes effectively neutral and unselectable, Crow's model breaks down completely, and there can be no effective selection strategy to stop mutation accumulation. Schoen et al. (1998) have modeled almost identical fitness decline curves arising from mutation accumulation.


# Man to the Rescue?

*Newsflash – Eugenics cannot stop degeneration, and cloning makes the mutation problem worse.*

Most informed geneticists would acknowledge that humans have a problem with genetic degeneration of the genome due to relaxed selection. They would probably acknowledge this problem extends to many other species and certainly to endangered species. They would probably also acknowledge the theoretical difficulties of establishing an effective selection scheme to stop the accumulation of genetic damage within the human population. However, many would also point out that the genetic degeneration process is gradual. With only a 1-2% decline in fitness per generation, they might say that the problem is not urgent. While it is true that the ultimate consequences of today's mutations will not be felt for many generations, it is equally true that the time to halt the overall genetic degeneration, if at all possible, would be now. As the problem becomes more advanced, genetic damage will get ahead of us, with a potential run-away (meltdown) situation developing. For those hedonists who live only for today, so what? But for those idealists who pin all their hopes on the survival and advance of the human race, this should be of great importance. They are likely to turn hopeful eyes to science and technology. Can human intervention triumph over the threat? The nature of genetic degeneration is

such that accumulating damage is inherently diffused throughout the genome. It cannot be dealt with one gene at a time. It should therefore be obvious that the laser-like precision of genetic engineering has nothing to offer. However, we might reasonably ask if artificial selection, or the emerging capacity to clone human beings, might not solve the problem.

## Eugenics to the rescue?

The general perception that man is degenerating is found throughout modern and ancient literature. All cultures have legends about "men of old" who were smart, powerful, and long-lived. Darwin's book, *The Origin of Species by Means of Natural Selection, or The Preservation of Favoured Races in the Struggle for Life*, introduced the new idea that strong and continuous selection might halt this perceived degenerative trend. He pointed to human efforts in animal and plant breeding as evidence. In his book *The Descent of Man*, Darwin went further, contending that there is a need for "superior" races (i.e., the white race) to replace the "inferior" races. This ushered in *modern* racism, which came to a head in Hitler's Germany. Before World War II, many nations, including America, had government-directed eugenics programs. These programs included forced sterilization of the "unfit" and aggressive promotion of abortion/fertility-control for the underclass. Ever since the time of Darwin, essentially all of his followers have been eugenicists at heart, and have advocated the genetic improvement of the human race. When I was an evolutionist, I was also, at heart, a eugenicist. The philosophers and scientists who created the modern "synthetic theory" of evolution were uniformly eugenicists. However, after the horrors of WWII, essentially all open discussions of eugenics were quietly put aside.

In light of a deteriorating genome, should eugenics be re-examined? Unfortunately, this is already happening, but it is neither morally nor scientifically defensible. The thesis of this book cannot logically be used to support eugenics, but strongly argues against it. The eugenicist's vision is an insidious delusion. No form of selection can stop genomic degeneration. This includes artificial selection. To attempt to artificially increase selection intensity globally would be physically, socially, and politically impossible. Only a ruthless, world-wide, authoritarian "power elite" could possibly dictate the standards for selection, deciding who could and who could not reproduce. Even if such an insidious plan could effectively be implemented, it would not stop genomic degeneration. Any potential genetic "progress" would be trivial, and would not be sufficient to offset the overall degeneration of the genome. "Inferiority" versus "superiority" is an ambiguous and very poorly inherited characteristic, and is largely influenced by non-genetic (environmental) factors (see Chapter 6). Selection for any non-genetic trait results in zero selective progress. Even selection for more "heritable" traits would be ineffective, because of all the genetic arguments I have just presented. "Fitness" is a very general term, and is affected by countless genes, most of which are minor or near-neutral. As we have been learning, effective selection can only act upon a handful of "significant" genes. It is true that we could artificially select for virtually any single human trait to make people taller or shorter, lighter or darker, or fatter or skinnier. But we could not effectively select for *superior*, which inherently involves thousands of genes and millions of nucleotides as well as a fair amount of subjectivity.

Any possible *benefit* of enhanced or artificial selection in man would be a slight improvement of a very limited number of very specific

traits. But the genome would still be "rusting out" at about the same overall speed. The *cost* of eugenics would be social and moral upheaval on a level that would be catastrophic. Eugenics was a racist concept at its inception, and has always been driven by the Primary Axiom. Eugenics is not genetically sound. Furthermore, it is tightly linked with authoritarian government, elitist philosophy, suppression of personal rights, and violation of human dignity. Eugenics cannot rescue us from genomic degeneration. If we foolishly try to rescue the genome in this way, who will then rescue us from the eugenicists?

## Cloning to the rescue?

To clone a human being means to take a cell from a mature (presumably superior) individual and to use that cell to produce one or more copies of that individual. The consequence of cloning would have profound genetic consequences. While I was still an evolutionist and was very concerned about the genetic degeneration of man, I naively believed that cloning might be the answer. I hoped that cloning might halt genomic degeneration, and might even allow rapid improvement of the human population.

In plant genetics, when a species is easily propagated, clonal selection provides the surest and fastest way to improve a population. Given this knowledge, perhaps it is surprising that clonal selection for man has not been more vigorously advocated. However, even apart from the moral and social problems associated with cloning, the best-case scenario for cloning would involve only short-term gains and would guarantee long-term genetic degeneration.

An unspoken theme of this book is that what is already known for clonal populations also applies to sexual populations. The proof that all clonal populations must degenerate genetically was first shown by Muller, and has been termed "Muller's ratchet" (Muller, 1964; Felsenstein, 1974). Within any clonal line, mutations will accumulate over time. Even selection within a clonal line for the *best sub-clones* does not stop the decline. The "ratchet" only works one way and all change must be downward. Each cell division adds mutations and there is no mechanism to take mutations away. Even allowing for some beneficial mutations, each beneficial mutant is always linked to many more deleterious mutations. Within clones, there is no mechanism to break this linkage between rare beneficial mutations and abundant deleterious mutations. The deleterious mutants will always grow in number faster than the beneficials, and they will always drag any beneficials down with them. Therefore, **net information must always decline**. To repeat, this applies to even the best, most highly selected sub-clones. The certainty of genomic degeneration in clonal populations is well known among geneticists. The reason there are still many populations of clonal plants (and some animals), appears to reflect the fact that there has not yet been enough time for such populations to degenerate to the point of extinction.

Preliminary animal cloning experiments indicate the cloning of animals cannot even produce short-term genetic gains. Cloned animals routinely display immediate and severe genetic damage. Why is this? Cloned animals routinely show evidence of mutational damage as if they are "pre-aged" (Hochedlinger et al., 2004). There are probably multiple reasons for this (genetic and epigenetic), but one major reason involves the fact that mutations continue to build

up within somatic cells. Normal reproductive cells are "designed" to undergo the least possible cell divisions between generations, thereby minimizing mutation accumulation per generation. It is for such reproductive cells that we have the minimal estimate of "just" 100 point mutations per person per generation. For somatic cells (at least for the continuously-dividing stem cells), the number of cell divisions is much higher than in the germline, and so the mutation rate should also be very much higher (sharply increasing with age). As we grow and then begin to age, every cell in our body becomes genetically more mutant and more "unique". It is impossible to keep a large genome unchanged, even within a clone! New mutations occur in every cell, at the rate of roughly *one mutation every cell division*. Therefore, essentially every single cell in our body is unique. For these reasons every human clone will always be inferior to the mature "source individual" from which they were cloned. Such a clone will in a sense be *pre-aged*, having the original mutational load of the source individual plus the mutational load that has accumulated during that person's growth and aging. Because of the many cell divisions during somatic development and stem cell maintenance, a human clone will be roughly comparable, in terms of degeneration, to individuals many sexual generations into the future. In this sense such a clone is like a foreshadowing of where the species is going. It is going down, not up (Figure 11).

There are powerful moral, social, and genetic arguments against cloning. Cloning can be viewed as a very high-tech form of eugenics with all its technical and moral problems. Eugenics in general, and cloning in particular, are definitely not solutions to genomic degeneration.

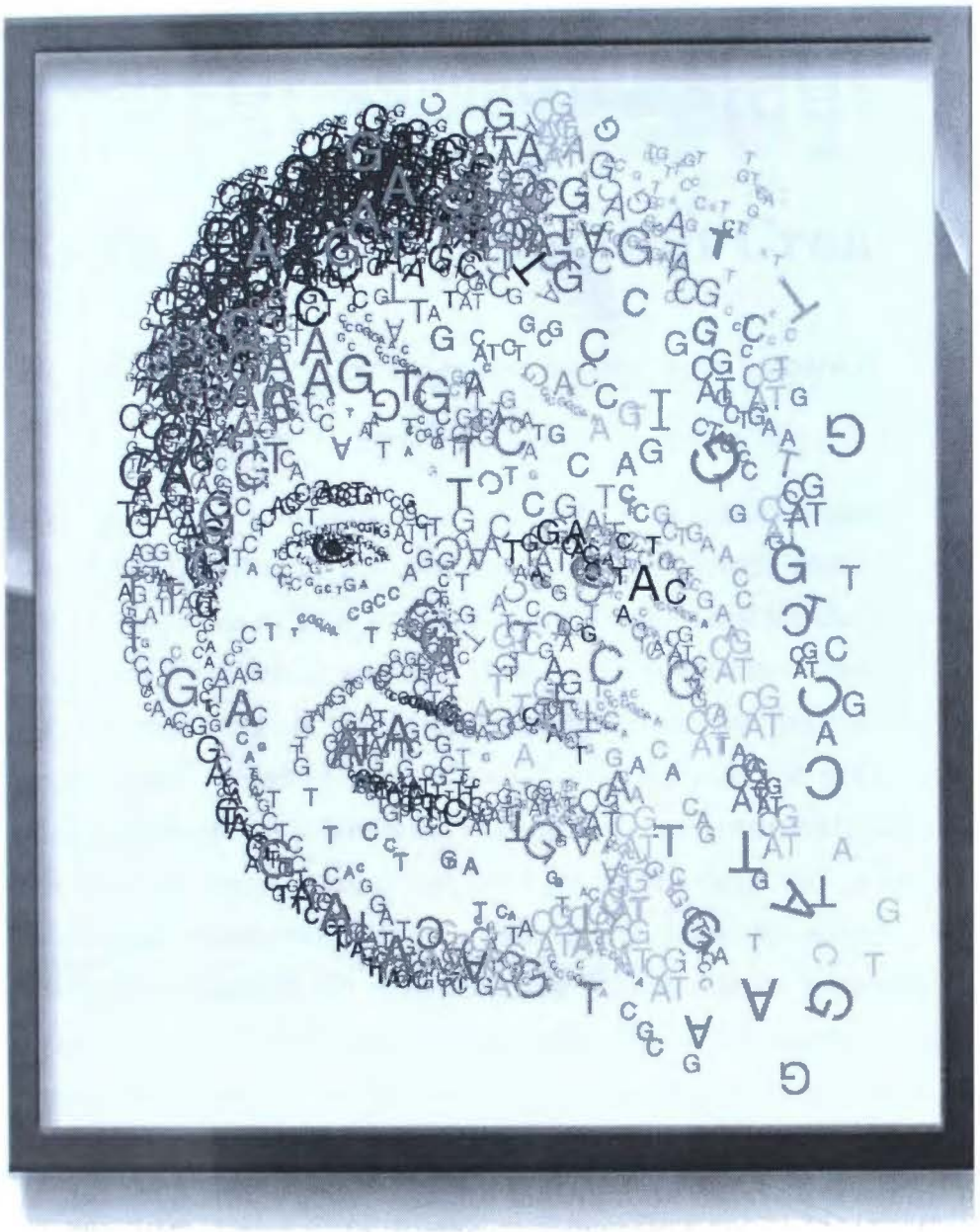


***Figure 11: Degeneration of the genome, degeneration of man, and degeneration of mankind.***

We experience it on a personal level, and we see it all around us. It is "genetic entropy" and there is nothing man can do to halt it. It is biologically inevitable. It is why species go extinct, and it is why we are all individually in the process of dying.

# Chapter 9

# Can Natural Selection Create?

*Newsflash – Mutation/selection cannot even create a single gene.*

We have been analyzing the problem of genomic degeneration and have found that the genome must degenerate regardless of how we analyze it. This problem overrides all hope for the forward evolution of the whole genome. However, some limited traits might still be improved via mutation/selection. Just how limited is such progressive ("creative") mutation/selection? From the perspective of our analogy, an instruction manual, we can intuitively see that not even a single component of a jet plane (let's say a molded aluminum component) could realistically arise by misspellings within the manual. So it is certainly reasonable to then ask the parallel question, "Could mutation/selection create even a single functional gene?" The answer is that it cannot, because of the enormous preponderance of deleterious mutations, even within the context of a single gene. The net information must always still be declining, even within a single gene. However, to better understand the limits of forward selection, let us for the moment *discount all deleterious mutations* and only consider beneficial mutations. Could mutation/selection *then* create a new and functional gene?

**1. Defining our first desirable mutation.** The first problem we encounter in trying to create a new gene via mutation/selection

is defining our first beneficial mutation. By itself, no particular nucleotide (A, T, C or G) has more value than any other, just as no letter in the alphabet has any particular meaning outside of the context of other letters. So selection for any single nucleotide can never occur except in the context of the surrounding nucleotides (and, in fact, within the context of the whole genome). A change of a single letter within a word or chapter can only be evaluated in the context of the surrounding block of text. This brings us to an excellent example of the principle of "irreducible complexity". In fact, it is irreducible complexity at its most fundamental level. We immediately find we have a paradox. To create a new function, we will need to select for our first beneficial mutation, but we can only define that new nucleotide's value in relation to its neighbors and we are going to have to be changing most of those neighbors also! We create a circular path for ourselves. We will keep destroying the "context" we are trying to build upon. This problem of the fundamental inter-relationship of nucleotides is called *epistasis*. True epistasis is essentially *infinitely complex*, and virtually impossible to analyze, which is why geneticists have always conveniently ignored it. Such bewildering complexity is exactly why language (including genetic language) can never be the product of chance, but requires intelligent design. The genome is literally a book, written literally in a language, and short sequences are literally sentences. Having random letters fall into place to make a single meaningful sentence, by accident, is numerically not feasible. The same is true for any functional strings of nucleotides. If there are more than several dozen nucleotides in a functional sequence, we know that realistically they will *never* just "fall into place". This has been mathematically demonstrated repeatedly. But as we will soon see, neither can such a sequence

arise randomly one nucleotide at a time. A pre-existing "concept" is required as a framework upon which a sentence or a functional sequence must be built. Such a concept can only pre-exist within the mind of the author. Starting from the very first mutation, we have a fundamental problem even in trying to define what our first desired beneficial mutation should be!

**2. Waiting for the first mutation.** Human evolution is generally assumed to have occurred in a small population of about 10,000 individuals. The mutation rate for any given nucleotide, per person per generation is exceedingly small (only about one chance in 30 million). So in a typical evolutionary population, if we assume 100 mutations per person per generation, one would have to wait 3,000 generations (at least 60,000 years) to expect a specific nucleotide to mutate within a population of 10,000. But two out of three times, it will mutate into the "wrong" nucleotide. So to get a specific desired mutation at a specific site will take three times as long, or at least 120,000 years. Once the mutation has occurred, it has to become *fixed* (such that all individuals in the population will have two copies of it). Because new mutations are so rare within the population, they have an extremely great probability of being *lost* from the population due to random genetic drift. Only if the mutation is dominant and has a very distinct benefit does selection have any reasonable chance to rescue it from random elimination via drift. According to population geneticists, apart from effective selection, in a population of 10,000, our given new mutant has only one chance in 20,000 (the total number of non-mutant nucleotides present in the population) of **not** being lost via drift. Even with some modest level of selection operating, there is a very high probability of random loss, especially if the mutant is recessive or

is weakly expressed (we actually know that almost all beneficial mutations will be both recessive and nearly neutral). For example, if a new mutation increases fitness by 0.5 percent, it only has a 1% probability of becoming fixed. The desired beneficial mutation will be randomly lost at least 99 out of 100 times. So a typical mildly-beneficial mutation must happen about 100 times before it is likely to "catch hold" within the population (even though it is beneficial!). On average, we would have to wait 120,000 x 100 = 12 million years to stabilize our typical first desired beneficial mutation to begin building our hypothetical new gene. So, in the time since we supposedly evolved from chimp-like creatures (6 million years), there would not be enough time to realistically expect our first desired mutation destined for fixation.

**3. Waiting for the other mutations.** After our first mutation has been found (the one that will eventually be fixed), we need to repeat this process for all the other nucleotides encoding our hoped-for gene. A gene is minimally 1,000 nucleotides long (this is really 50-fold too generous as I am ignoring all regulatory elements and introns). So if this process was a straight, linear, and sequential process, it would take about 12 million years x 1,000 = 12 billion years to create the smallest possible gene. This is approximately the time since the reputed Big Bang! So it is a gross understatement to say that the rarity of desired mutations limits the rate of evolution!

**4. Waiting for recombination.** Because sexual species (such as man) can shuffle mutations, it might be thought that all the needed mutations for a new gene might be able to occur simultaneously within different individuals within the population, and then all the

desirable mutations could be "spliced together" via recombination. This would mean that the mutations would not have to occur sequentially, thus shortening the time needed to create the hoped-for gene (so we might need less than billions of years). There are two problems with this. First, when we examine the human genome, we consistently find the genome exists in large blocks (20,000-40,000 nucleotides) within which no recombination has occurred *since the origin of man* (Gabriel et al., 2002; Tishkoff and Verrelli, 2003). This means that virtually no meaningful shuffling is occurring on the level of individual nucleotides. Only large gene-sized blocks of DNA are being shuffled. I repeat, no actual nucleotide shuffling is happening! Second, even if there were effective nucleotide shuffling, the probability of getting all the mutants within the population to shuffle together into our hoped-for sequence of 1,000 is so astronomically remote that we would need even *more* time than is needed for the sequential approach (even *more* billions of years) for this scenario to work. Lastly, if there really *were* a type of nucleotide shuffling that could build a new gene in this way, it would be torn apart again by the same extensive nucleotide shuffling in the very first generation after the new gene fell into place. In poker, it is not likely you will be dealt a royal flush. If you are, what are the odds you will then get that very same hand dealt to you again after the cards are reshuffled?

**5. Waiting on "Haldane's dilemma".** Once that first mutation destined to become fixed within the population has finally occurred, it needs time to undergo selective amplification. A brand new mutation within a population of 10,000 people exists as only one nucleotide out of 20,000 alternatives (there are 20,000 nucleotides at that site, within the whole population). The mutant nucleotide

must "grow" gradually within the population, either due to drift or due to natural selection. Soon there might be two copies of the mutant, then four, then 100, and eventually 20,000. How long does this process take? For dominant mutations, assuming very strong unidirectional selection, the mutant might conceivably grow within the population at a rate of 10% per generation. At this very high rate, it would still take roughly 105 generations (2,100 years) to increase from 1 to 20,000 copies ($1.1^{105} = 20{,}000$). However, mutation fixation takes much longer than this because selection is generally very weak, and most mutations are recessive and very subtle. When the mutation is recessive, or when selection is not consistently unidirectional or strong, this calculation is much more complex, but it is obvious that the fixation process would be dramatically slower. For example, an entirely recessive beneficial mutation, even if it could increase fitness by as much as 1%, would require at least 100,000 generations to fix (Patterson, 1999).

Haldane (1957), calculated that it would take (on average) 300 generations (>6,000 years) to select a single new mutation to fixation, given what he considered a "reasonable" mixture of recessive and dominant mutations. Selection at this rate is so slow that it is essentially the same as no selection at all. This problem has classically been called "Haldane's dilemma". At this rate of selection, one could only fix 1,000 beneficial nucleotide mutations within the whole genome in the time since we supposedly evolved from chimps (6 million years). This simple fact has been confirmed independently by Crow and Kimura (1970), and ReMine (1993, 2005). The nature of selection is such that selecting for one nucleotide reduces our ability to select for other nucleotides (selection interference). *Simultaneous selection does not help.*

At first glance, the above calculation seems to suggest that one *might* at least be able to select for the creation of one *small* gene (of up to 1,000 nucleotides) in the time since we reputedly diverged from chimpanzee. There are two reasons why this is not true. First, Haldane's calculations were only for independent, unlinked mutations. Selection for 1,000 *specific and adjacent* mutations could not happen in 6 million years because that specific sequence of adjacent mutations would never arise, not even in 6 *billion* years. One cannot select mutations that have not happened. Second, the vast bulk of a gene's nucleotides are near-neutral and cannot be selected at all–not in *any length of time.* The bottom line of Haldane's dilemma is selection to fix new beneficial mutations occurs at glacial speeds, and the more nucleotides under selection, the slower the progress. This severely limits progressive selection. Within reasonable evolutionary timeframes, we can only select for an extremely limited number of unlinked nucleotides. In the last 6 million years, selection could maximally fix 1,000 unlinked beneficial mutations, creating less new information than is on this page of text.* There is no way that such a small amount of information could transform an ape into a human.

Although we have temporarily suspended deleterious mutations from consideration, it is fair to note that, since the hypothetical time when human and chimps diverged, geneticists believe that many thousands of deleterious mutations should have been fixed

** In terms of information content, three nucleotides equal roughly one typewritten character (there are only 4 nucleotides, but 26 letters, and more than 64 keys on a keyboard). So one codon triplet equals roughly one typographical letter, and thus 1000 nucleotides equals only 333 characters on a typewritten page.*

via genetic drift (Kondrashov, 1995; Crow, 1997; Eyre-Walker and Keightley, 1999; Higgins and Lynch, 2001). Evolutionary assumptions should lead to the logical conclusion that we have significantly degenerated from our ape-like ancestors. The power of this logic is overwhelming. In fact, we know man and chimp differ at roughly 150 million nucleotide positions (Britten, 2002), due to at least 40 million hypothetical mutations. Therefore, if we assume man evolved from a chimp-like creature, during that process there must have been about 20 million nucleotide fixations within the human lineage (40 million divided by 2), but natural selection could only have selected for ~1,000 of these. All the rest would have had to have been fixed by random drift, resulting in millions of nearly-neutral deleterious substitutions. The result? A maximum of 1000 beneficial substitutions and millions of deleterious substitutions. This would not just make us inferior to our chimp-like ancestors, it would obviously have killed us!

**6. Endless fitness valleys.** Evolutionists agree that the creation of a new gene requires a great deal of experimentation. During the construction phase of developing a new gene, we have to expect a period of time when the experiment reduces a species' fitness. This is a *fitness valley*. A half-completed gene is neither beneficial nor neutral. It is going to be deleterious. In a sense, the species has to get worse before it can get better. It is easy to imagine a species surviving fitness valleys if they are brief and if they are rare.

Deep fitness valleys are likely to lead to extinction. The rarity of good mutations in combination with Haldane's dilemma should make fitness valleys indefinitely long and deep. Continuous evolutionary innovation would make a species' fitness decline with

no end. Life would be just one fitness valley upon another. The super-highway of evolution would always be under construction, and total fitness would always be declining rather than increasing. The concept of a species passing through fitness valleys makes evolutionary sense only when individual traits are considered. However, when the whole genome is considered, the concept of indefinitely numerous and indefinitely long fitness valleys argues strongly against the evolution scenario.

**7. Poly-constrained DNA.** Most DNA sequences are *poly-functional* and so must also be *poly-constrained.* This means that DNA sequences have meaning on several different levels (poly-functional) and each level of meaning limits possible future change (poly-constrained). For example, imagine a sentence which has a very specific message in its normal form but with an equally coherent message when read backwards. Now let's suppose that it also has a third message when reading every other letter, and a fourth message when a simple encryption program is used to translate it. Such a message would be poly-functional and poly-constrained. We know that misspellings in a normal sentence will not normally improve the message, but at least this would be *possible.* However, a poly-constrained message is fascinating, in that it cannot be improved. It can *only* degenerate (see Figure 12, p. 142). Any misspellings which might possibly improve the normal sentence form will be disruptive to the other levels of information. *Any change at all* will diminish total information with absolute certainty.

There is abundant evidence that most DNA sequences are poly-functional, and are, therefore, poly-constrained. This fact has been

extensively demonstrated by Trifonov (1989). For example, most human coding sequences encode for two different RNAs that read in opposite directions (i.e., both DNA strands are transcribed–Yelin et al., 2003). Some sequences encode for different proteins, depending on where translation is initiated and where the reading frame begins (i.e., read-through proteins). Some sequences encode for different proteins based upon alternate mRNA splicing. Some sequences serve multiple functions simultaneously (i.e., as a protein-coding sequence and as an internal transcriptional promoter). Some sequences encode for both a protein coding region and a protein-binding region. Alu elements and origins of replication can be found within functional promoters and within exons. Basically all DNA sequences are constrained by isochore requirements (regional GC content), "word" content (species-specific profiles of di-, tri-, and tetra-nucleotide frequencies), and nucleosome binding sites (because all DNA must condense). Selective condensation is clearly implicated in gene regulation, and selective nucleosome binding is controlled by specific DNA sequence patterns that must permeate the entire genome. Lastly, probably all sequences also affect general spacing and DNA-folding/architecture, which is clearly sequence dependent. To explain the incredible amount of information which must somehow be packed into the genome (given the extreme complexity of life), we really have to assume that there are even higher levels of organization and information encrypted within the genome. For example, we know there is another whole level of organization at the epigenetic level (Gibbs, 2003). There also appears to be extensive, sequence-dependent, three-dimensional organization within chromosomes and within the whole nucleus (Manuelidis, 1990; Gardiner, 1995; Flam, 1994). Trifonov (1989) has shown that probably all DNA sequences in the genome encrypt multiple codes (up to 12). In computer science,

this type of data compression can only result from the highest level of information design and results in maximal information density. These higher levels of genomic organization/information content, greatly multiply the problem of poly-constrained DNA. Every nucleotide interacts with many other nucleotides, and everything in the genome seems to be context-dependent. The problem of ubiquitous, genome-wide, poly-constrained DNA seems absolutely overwhelming for evolutionary theory. Changing *anything* seems to potentially change *everything*! The poly-constrained nature of DNA serves as strong evidence that higher genomes cannot evolve via mutation/selection except on a trivial level. Logically, all poly-constrained DNA had to be designed.

**8. Irreducible complexity.** The problem of irreducible complexity has been brilliantly presented by Behe (1996). He has illustrated the concept of irreducible complexity in various systems that have multiple components, such as a mousetrap design which requires 5 independent parts, or a flagellum having perhaps 10-20 component parts. His idea is that each *part* has no value except within the context of the *whole* functional unit, and so irreducible systems have to come together all at once and cannot arise one piece at a time. In the case of a mousetrap, all the pieces may have been sitting next to each other on the inventor's workbench but they would not have come together by chance, or by any realistic evolutionary progression. They came together as a *synthesis*, simultaneously, in the mind of the inventor. It is in the realm of *mind* that deep complexity comes together and becomes integrated.

In our example of the evolution of transportation technology, the simplest first improvement we might imagine might be the occurrence of misspellings that would convert our red wagon into a

blue tricycle. It is indeed easy to imagine a misspelling that might cause the paint code to be changed (although the blue paint would have to already be available, and coded). Likewise, a misspelling could certainly cause a wheel to fall off. However, a three-wheeled wagon is not a tricycle. It is a broken wagon. To convert a wagon to a tricycle would require extensive reworking of the instruction manual and radical changes in most of the component parts. There would be no intermediate functional steps to accomplish these complex changes, and so no prospect for our quality control agent to selectively help the process along. In fact, he would be selecting against all our desired misspellings and changes. So the correct combination of misspellings would have to arise simultaneously by chance, all at the same time, which would never happen. Obviously, a tricycle could only arise from a wagon by way of intelligent and extensive reworking of the design and a thorough re-writing of the instruction manual (see Figure 13, p. 143).

Although a wagon or tricycle may have dozens of component parts, even the simplest protein is much more complex, having hundreds of component parts, and achieving a level of irreducible complexity profoundly greater than that illustrated by our wagon analogy. As the number of components of a design increases linearly, the number of *interactions* (hence the complexity) increases exponentially.

As complex as proteins are, underlying every protein is a genetic system comprising even higher levels of irreducible complexity. The molecular machinery underlying the coding, transcription, and translation of a protein is phenomenal. Ignoring all the other accessory proteins involved, just the design of the DNA/RNA sequence is mind-boggling. Although a simple protein has a few

hundred component parts, the underlying gene that produces it has thousands of component parts. All of these parts are interacting and mutually-defining. Each nucleotide has meaning only in the context of all the others. Each nucleotide is poly-functional, interacting with many other nucleotides. The DNA sequence defines regional 3-D chromatin structure, local protein binding, uncoiling, transcription, and also defines one or more RNA sequences. The RNA sequence defines RNA stability, RNA variable splicing, RNA processing, RNA transport, transcription efficiency, and protein sequence.

We do not yet really understand how any single gene from a higher life form really works in its entirety, especially in the context of everything else that is happening in the cell. A single gene with all its interactions is still way too complex for us. When we consider the full complexity of a gene, including its regulatory and architectural elements, a single gene has about 50,000 component parts. I presume that this is more component parts than are found in a modern automobile. There is no simple linear path that leads car components to spontaneously become a functional car. *Mind* is obviously required (actually, *many*, brilliant minds). In the same way, there is no linear path of selection that can build a single gene from its individual nucleotides. A *mind* is likewise required. **Yet a single gene is just a microscopic speck of irreducible complexity within the universe of irreducible complexity comprising a single cell. Life itself is the very essence of irreducible complexity, which is why we cannot even begin to think of creating life ourselves. Life is layer upon layer of irreducible complexity.** Our best biochemical flow charts, of which we are so proud, are just childish cartoons of true biological

complexity, for this is something we cannot even comprehend. It is a tribute to the mind of man that we have started to understand how even a single gene works, and that we can now design and build very small artificial genes. But we still cannot design a new gene for a new and unknown protein, which could then precisely integrate into the complexity of a higher life form. If we cannot do this, why would we think that random mutations, combined with a very limited amount of reproductive sieving, could accomplish this? For the reader's interest I have attempted to expand upon the concept of irreducible complexity with the concept of Integrated Complexity (see Appendix 3).

**9. Almost all beneficial mutations must be nearly neutral.** We have already discussed at length the difficulty of selecting against near-neutral deleterious mutations, and this problem is begrudgingly acknowledged by most geneticists. However, there is an important flip side to this problem that I have *never* heard acknowledged. As we have already discussed in Figure 3d (p. 32), the problem of near-neutrality is much more severe for beneficial mutations than for deleterious mutations. Essentially *every* beneficial mutation must fall within Kimura's "no-selection zone". All such mutations can *never* be selected for. This problem multiplies all of the problems I have already outlined above. Our hoped-for new gene will certainly have a *few* nucleotides that have major effects. For example, the ones that specify the active site of an enzyme. But such nucleotides can only have major effects within the context of the whole protein and the whole gene sequence. The whole protein/gene is constructed primarily with components that individually have only a small impact on the whole unit, and have only a miniscule impact on the fitness of

the whole individual. In combination, these nucleotides contain most of the information contained within the gene. Without them the "important nucleotides" are meaningless. Yet they are all individually unselectable. So how can we establish them and keep them in their respective places during gene construction? The answer is obviously that we simply cannot. And apart from these "insignificant masses" of nucleotides the elite "important nucleotides" cannot be selected for either. Because of the near-neutral problem, we cannot even get to first base in terms of building our hoped-for new gene. The entire framework of the new gene is defined by the near-neutrals, but there is no way to either put them or hold them in place. The near-neutral nature of beneficial mutations is strong evidence that every gene had to be designed, and that there is simply no conceivable way to build a gene one nucleotide at a time via selection.

**10. Putting bad mutations back in the picture.** We have briefly considered a variety of powerful arguments about why progressive mutation/selection must be very limited in its scope. These arguments have temporarily excluded from consideration all deleterious mutations. However, in reality, progressive selection must occur in the real world, where deleterious mutations outweigh beneficial mutations by perhaps a million to one. To be honest, we must now re-introduce deleterious mutations.

a) Muller's ratchet – As I mentioned earlier, when we study the human genome, we see that large blocks of DNA have essentially no historical evidence of recombination (Gabriel et al. 2002; Tishkoff and Verrelli, 2003). Recombination appears to be primarily between genes rather than between nucleotides. So within any limited gene sequence there is essentially no recombination. Any such block of DNA that

does not have recombination is subject to "Muller's ratchet" (Muller, 1964; Loewe, 2006). This means that the good mutations and the bad mutations cannot be separated. Since we know that the bad mutations overwhelmingly outnumber the good, we can be certain that any such stretch of DNA must degenerate. The hordes of bad mutations will always drag the rare good mutations down with them. While we are waiting for a rare beneficial mutation, bad mutations are piling up throughout the region. Even if we could succeed in accumulating perhaps a hundred "good" mutations within a region, and were waiting for the next one to come along, we would start to see many of our good mutations start to back-mutate into the bad. Time is our enemy in this situation. The more time, the less information. Muller's ratchet will *kill* a new gene long before it can take shape.

b) Too much selective cost – In previous chapters we have discussed the *cost of selection.* Haldane's dilemma only considers progressive selection. But we can only afford to "fund" progressive selection for beneficial mutations after we have paid for all other reproductive costs, including all costs associated with eliminating bad mutations. As we have already seen, there are so many bad mutations we cannot afford even to pay the reproductive cost of eliminating *them.* Since we cannot afford to stop degeneration, we obviously have nothing left over to fund progressive selection. There is just one way around this. In the short run, we *can* fund progressive selection for a very limited number of traits if we borrow "selection dollars" from our long-term struggle against bad mutations. However, we need to understand that this means that any short-term progress in terms of specific beneficial mutations is paid for by faster genomic degeneration in the long run.

c) Non-random mutation – As it turns out, mutations are not entirely random. Can this help us to create new genes? No, it makes our problem much worse! For example, we now know that some nucleotide positions are much more

> likely to mutate than others ("hotspots"), and that certain nucleotides are favored in substitutions. Mutational "hot spots" will give us the mutant we want sooner in that location, but while we then wait for the complementary mutations within the "cold spots", the hotspots will proceed to back-mutate again. We are forced to keep re-selecting our good mutations within the hot spots, while we wait for even the first good mutation to occur within the cold spots. This makes things worse, rather than better. The greater tendency to mutate to a certain nucleotide, (let's say *T*), will help us in positions where *T* is desired, but it will slow us down whenever *G, C, or A* is desired. Therefore, *75% of the time the bias toward T mutations will slow down progressive selection.* "Non-random mutation" sounds good from the point of view of building information, but unfortunately we are not talking about the non-randomness of *design.* Rather, we are talking about a type of non-randomness which (ironically) is antithetical to information building.

**We have reviewed compelling evidence that, even when ignoring deleterious mutations, mutation/selection cannot create a single gene within the human evolutionary timescale. When deleterious mutations are factored back in, we see that mutation/selection cannot create a single gene, ever. This is overwhelming evidence against the Primary Axiom.** ***In my opinion this constitutes what is essentially a formal proof that the Primary Axiom is false.***

In conclusion, the genome must have been designed, and could not have evolved. Yet we all know that micro-evolution (adaptive selection) *does* happen. How can this be? To use the terminology of our earlier chapters, mutations are the dings, scratches, and broken parts of life. Therefore, I believe most useful variation must be *designed.* When we see adaptive selection occurring, we

are usually witnessing segregation and recombination of useful variants of genes and gene components that were designed to segregate and recombine in the first place. We are not usually seeing the result of random mutations, which are consistently deleterious. Selection operates to eliminate the worst of mutations, while favoring the most desirable recombinants and segregants of designed variation. For example, a single human couple, if they contained designed and functional heterozygosity at only a tiny fraction of their nucleotides, would produce (via recombination and segregation) an essentially unlimited range of useful diversity. It is this type of designed diversity that natural selection can act upon most effectively. All such designed variants would be expected to be created within useful linkage groups, and would have originated at high allelic frequencies. For example, in the case of a single human couple, there could be only four initial sets of chromosomes, so all initial nucleotide frequencies would be at least 25%. Functional linkage groups and high allele frequency allow for very rapid responsiveness to selection, and thus rapid local adaptation. Like an ordered deck of cards, the net information in such a scenario would be greatest at the beginning, but diversity would be greatest only after many hands had been played out. Except at the beginning, no new information would be required.

*Author's note: In 2007 Michael Behe published his second book "The edge of Evolution", While his first book was based largely on theoretical considerations, this new book reviews massive amounts of empirical molecular data associated with three medically important microorganisms (the AIDS virus, the Malaria pathogen, and the E. coli bacteria). These systems are known to be highly mutable and undergo massive numbers of selection cycles, and are cited as powerful examples of "evolutionary systems". Behe shows that while these organisms rapidly adapt to new external conditions, they do not innovate any new internal functions. Even within these "ideal evolutionary systems", the type of change being documented only represents "fine-tuning", not true innovation. Although scientists have tracked these model systems though a vast number of reproductive cycles (many more than could occur even through "deep time" for higher organisms), all the observed changes have been merely "stop-gap measures". Behe powerfully demonstrates that the Primary Axiom cannot create irreducible complexity even on the simplest level.*


***Figure 12: Poly-constrained information and poly-constrained DNA.***

Like puns, palindromes, and other word puzzles, DNA contains poly-functional letters, words, and phrases. Such sequences can only arise by very careful *design*. Once they are created, they cannot be "mutated" to make them better. An excellent example is the painstakingly crafted poly-functional Latin phrase shown above (see Ohno and Yomo, 1991). This ancient word puzzle (dating back to 79 AD) has a translation something like, "THE SOWER NAMED AREPO HOLDS THE WORKING OF THE WHEELS." It reads the same, four different ways: left to right, up to down, and starting at the lower right, down to up, right to left. Any single letter change in this system destroys all four messages simultaneously (all four of which happen to be the same in this example). Similarly, a simple sentence palindrome would be: ABLE WAS I ERE I SAW ELBA, which reads the same forward or backwards. Any letter change destroys both messages. A simple example of a poly-functional word would be *LIVE*, which backwards is *EVIL*. To change *LIVE* to *HIVE* might be desirable, but it turns *EVIL* which has meaning, to *EVIH*, which is meaningless. So this dual-meaning word, like the other examples above, is poly-constrained, precisely because it is poly-functional.

## *Figure 13: Irreducible complexity.*

In our red wagon example, the simplest improvement one might imagine would be some misspellings that would convert our red wagon into a blue tricycle. This seemingly small evolutionary step forward could never happen by chance because it requires creation of many new components, each of which represents "irreducible complexity". It is not hard to imagine a misspelling that would change the paint code or cause a wheel to fall off. However, to make an operational tricycle that actually *works* requires extensive re-working of most of the components. Just one new component–the pedal apparatus–illustrates this. Creation of an operational pedal apparatus for our little red wagon could not arise from a few misspellings. *Several entirely new chapters* in the manual would be required for manufacturing and assembling the various components. But the new pedal apparatus would still not work without a place for one to sit and a place for one's legs! Very obviously, the corruption of a wagon's assembly manual via random misspellings (even with the help of our quality control agent) could never result in a shiny new blue tricycle. It could only lead to a run-down and broken wagon.

Chapter 10

# Is the Downward Curve Real?

*Newsflash – All evidence points to human genetic degeneration.*

Under Dr. Crow's most optimistic (and entirely unrealistic) selection model, we still see "backwards evolution", with a disastrous decay curve for the fitness values of all the individuals within a population (Figure 10b, p. 113). The rate of decline in that illustration is very consistent with Dr. Crow's own estimate that the fitness of the human population is now degenerating 1-2% per generation (Figure 4, p. 65). When Crow's model is corrected to be more realistic, allowing for differences between individual mutations, I do not believe the downward trend will ever level off.* But even if we do not correct Crow's model, it still shows genetic decay and declining fitness, rather than evolutionary progress.

The nature of information and the correctly formulated analogy of the genome as an instruction manual help us see that the genome must degenerate. This common-sense insight is supported by information theory (Gitt, 1997). The very consistent nature of mutations to erode information helps us see that the genome must deteriorate. The high rate of human mutation indicates that man

**Author's note: This has now been confirmed by numerical simulation (Sanford et al., 2007b).*

must be degenerating. The prohibitive cost of selecting for large numbers of mutations simultaneously indicates that man must be degenerating. The problems of near-neutral mutations, selection threshold, and selection interference, all indicate that man must be degenerating. Even realistic modeling and numerical simulation show that we are degenerating.

For decades biologists have argued on a philosophical level that the very special qualities of natural selection can essentially reverse the biological effects of the second law of thermodynamics. In this way, it has been argued, the degenerative effects of entropy in living systems can be negated, making life itself potentially immortal. However all of the analyses of this book contradict that philosophical assumption. Mutational **entropy** appears to be so strong within large genomes that selection cannot reverse it. This makes eventual extinction of such genomes inevitable. I have

*Author's note: The term entropy has several uses. I am using the term entropy as it is most commonly used, i.e.,* ***the universal tendency for things to run down or degrade apart from intelligent intervention.*** *Genetic entropy specifically means entropy as it applies to the genome. It reflects the inherent tendency for genomes to degenerate over time apart from intelligent intervention. Genetic Entropy is directly related to physical entropy, as this term is formally used by engineers and physicists. Mutations are the result of physical entropy being manifested on the molecular level. It is due to random atomic forces and imperfect operation of the "nanomachines" affecting DNA replication and DNA repair. Natural selection itself can be viewed as a type of mechanical apparatus that reduces mutational entropy by filtering out certain mutations. Like all machines, the bio-machinery affecting DNA replication, DNA repair, and selective elimination, all operate at less than 100% efficiency (mechanical inefficiency is a measure of entropy). Therefore, traditional entropy, in its most formal sense, lies at the root of both "mutational entropy" and "selection inefficiency", and together these lie at the root of Genetic Entropy.*

termed this fundamental problem **Genetic Entropy**. Genetic Entropy is not a starting axiomatic position, rather it is a logical conclusion derived from careful analysis of how selection really operates.

If the genome must degenerate, then the Primary Axiom is wrong. It is not just implausible. It is not just unlikely. It is absolutely dead wrong. It is not just a false axiom. It is an unsupported and discredited hypothesis, and can be confidently rejected. Mutation/selection cannot stop the loss of genomic information, let alone *create* the genome! Why is this? It is because selection occurs on the level of the whole organism. It cannot stop the loss of information (which is immeasurably complex) due to mutation, and is happening on the molecular level. **It is like trying to fix a computer with a hammer. The microscopic complexity of the computer makes the hammer largely irrelevant. Likewise, the microscopic complexity of genomic mutation**

*Caution: The term "Shannon entropy" will be used by some to confuse the issue of genetic entropy. Shannon entropy is an unfortunate and misleading term which was coined to refer to certain statistical properties of potential information. It is a way to measure the "surprise value" of a letter within a string of letters. Any simple repeating pattern reduces a string's Shannon entropy value. A high Shannon information value can reflect either a randomized set of letters or a carefully written poem! In other words high Shannon entropy values can reflect either intelligent design or random chaos. It is not a useful term in the context of this discussion. High Shannon entropy merely says, "there is no simple repeating pattern here." It is a term which is used in a very limited and specific sense and is not productively applied to biological information systems. It can only be used to deliberately cloud our understanding of the genome and its decay. Shannon himself warned against applying his terminology to biological systems.*

**makes selection on the level of the whole individual largely irrelevant.**

In our first chapter we considered a closely analogous scenario, wherein we tried to advance transportation technology. We proposed using a robotic, nearly-blind "scribe" who makes misspellings within instruction manuals at the beginning of a car-manufacturing plant. We then added a robotic, nearly-blind "judge" who does quality control at the other end of the assembly line. No humans *ever* enter the plant. We asked, "Will the cars coming off the assembly line get progressively better or worse?" Will the cars evolve into spaceships? Everything we have been considering should make it obvious. The cars will not evolve into spaceships. In fact, they will become progressively inferior cars. The quality control robot can at best delay the inevitable failure of the business. Does more time help in this scenario? No, infinite time would just give us infinite certainty that the system would fail. But our factory has neither infinite time nor infinite resources. Real life is like a business, and it must continually "pay all its costs" or go out of business (die).

Despite massive amounts of mental conditioning of the public by our educational institutions, I believe most people can still instinctively see that the relentless accumulation of random misspellings within assembly manuals cannot transform a car into a spaceship. Our quality control agent will **never, ever** see a deviant car that has a rocket engine, no matter how long he waits, nor how many misspellings occur in the manual. This is because of probability and because of the problem of irreducible complexity, as described by Behe (1996). Even if the judge **did** see a deviant

car with a rocket engine, he would have to reject it because a car with a rocket engine is still not a better means of transportation. Our judge (natural selection) has an I.Q. of zero, has zero foresight, and has no concept of what a spaceship might be. Therefore he (it) has no conception of the deviations needed to make a car more like a spaceship, nor would he (it) ever select such deviations. The only possible way he (it) could select toward a *spaceship* would be by selecting for better *cars,* which is clearly paradoxical. Even if our judge **could** begin to select for more "spaceship-like" cars (most emphatically he cannot), it would take such an astronomically huge number of misspellings to create a functional spaceship that it would essentially take forever. But remember, our car factory cannot afford to take forever. It has to pay its bills today. In fact, those cars that might be more "spaceship-like" would likewise be less "car-like". In other words they would be dysfunctional products, analogous to biological monstrosities. Bankruptcy is just around the corner for any such a commercial enterprise. Careful analysis, on many levels, consistently reveals that the Primary Axiom is absolutely wrong.

Would any one of you care to invest your life savings in a new company that had decided to use the mutation/selection manufacturing scheme? Its promoters say that it will be all robotic. No human agents will be needed at the plant, and they assure us that the plant will just keep making better and better products. Remember, we are not talking about a separately-funded research and development program. We are talking about a revenue-generating, boom or bust assembly line! Any buyers? I would certainly dismiss this as a fraud. Despite glossy brochures and VIP endorsements, I know that any such scheme could only make deteriorating cars, and could never produce a revolutionary

new spaceship. I have better places where I will invest my life and my life-savings.

If the Primary Axiom is wrong, then our basic under-standing of life history is also wrong (see Appendix 5). If the genome is degenerating, our species is not evolving. There appears to be a close parallel between the aging of a species and the aging of an individual. Both seem to involve the progressive accumulation of mutations. Mutations accumulate both within our reproductive cell lines and our body cell lines. Either way, the misspellings accumulate until a threshold is reached when things rapidly start to fall apart. This results in a distinct upper range for lifespan. Human life expectancy presently has an average of about 70 years with a maximum near 120. However, when first cousins marry, their children have a serious reduction of life expectancy. Why is this? It is because inbreeding exposes the genetic mistakes within the genome (recessive mutations) that have not yet had time to "come to the surface". Inbreeding is like a sneak-preview of where we are going genetically as a species. The reduced life expectancy of inbred children reflects the overall aging of the genome, and reveals the hidden reservoir of genetic damage (recessive mutation) that has been accumulating. If all this genetic damage were exposed suddenly (if we were all made perfectly inbred and homozygous), it would be perfectly lethal. We all would be dead. Our species would instantly become extinct.

**Genetic damage results in aging, and aging shortens lifespan. This is true for the individual and for the population**. Logically we should conclude that if all of this is true, then at some time in the past there must have been a time when there was less genetic damage in the genome, and thus longer

lives, and less deleterious effects from inbreeding. Is there any evidence of this?

The Bible records a limited time when people had extremely long lives, and when inbreeding was entirely benign. In fact, the life expectancies recorded in the book of Genesis seem unbelievable. According to the Bible, in the beginning, people routinely lived to be more than 900 years old! From where we stand now, that seems absurd. But our perspective, and our understanding, are so very limited! *We still do not know* why most mammals have a maximal lifespan of less than 20 while man's is about 120 years. Even chimps have a maximal life-expectancy less than half that of man. However, we *know at least this much: mutation is clearly implicated in aging.* So if there were initially no mutations, wouldn't you expect the maximal human age to be much longer? From this perspective, apart from mutations, human ages of hundreds of years would not be so crazy. They would be logical. Indeed, why would we die sooner?

A recent paper by a mathematician and a theologian presents some fascinating data (Holladay and Watt, 2001). Their paper compares the lifespan of early Biblical characters to how many years they were born after the patriarch Noah. This Biblical data (recorded thousands of years ago) clearly reveals an exponential decay curve. This curve can only be described as biological. The calculated line of best fit is exponential and corresponds to the actual Biblical data very closely (correlation coefficient = 0.94). The actual formula for the decay curve that best fits the data was $y = 386.6835\ (e^{-0.00462214x}) + 70.065$. I have done a similar analysis (Figure 14, p. 155).

This unexpected trend in the Biblical data is amazing. We are forced to conclude that the writer of Genesis either faithfully recorded an exponential decay of human life spans or fabricated the data using sophisticated mathematical modeling. To fabricate this data would have required an advanced knowledge of mathematics, as well as a strong desire to show exponential decay. But without knowledge of genetics (discovered in the 19th century), or mutation (discovered in the 20th century), why would the author of Genesis have wanted to show a biological decay curve? It does not seem reasonable to attribute this data to some elaborate stone-age fraud. The most rational conclusion is that the data are real, and that human life expectancy was once hundreds of years, but has progressively declined to current values. The most obvious explanation for such declining life spans, in light of all the above discussions, would be genetic degeneration due to mutation (the downward curve is especially steep in the early generations, suggesting that at that time there may have been a substantially elevated mutation rate).

In conclusion, we can see that even using Crow's most optimistic model, the downward curve for fitness is real, and in fact closely matches the downward curve for life spans recorded in the book of Genesis. The *bad news* is that our species, like we ourselves, is dying. The Primary Axiom is wrong. Information decays. Genomes decay. Life is not going up, up, up. It is going down, down, down. Selection does not create information, and at best can only slow its decay.

**Information.** Genetic information *must* erode over time. The actual rate for *all types* of mutations may be more than 600 per

person per generation. Given a diploid genome size of 6 billion, *we should be losing about one ten millionth of our total information per generation* (this number is not affected by what fraction of the genome is actually functional). To the extent that we are thinking linearly, this does not sound very shocking. After all, we might think that to lose 100% of the information would take ten million generations. However, information is not linear. *A major computer program can fail completely due to a single error.* A very robust program can withstand multiple errors, but even the best designed programs cannot tolerate large numbers of errors. The genome appears to be so well designed it can tolerate tens of thousands of errors. It is amazingly robust and unlike anything ever designed by man. But the genome is still not immune to failure due to error accumulation. If the rate of loss was constant and at its current level for 300 generations (6,000 years), we would lose about 0.003% of our total information. This is *huge* (90,000 errors), yet it is *conceivable* given the extremely robust nature of the genome. However, if we continued to lose information at this same rate for 300,000 generations (6 million years) we would lose 3% of all our information! This would represent 90 million errors! This is inconceivable. No program could still be functional.

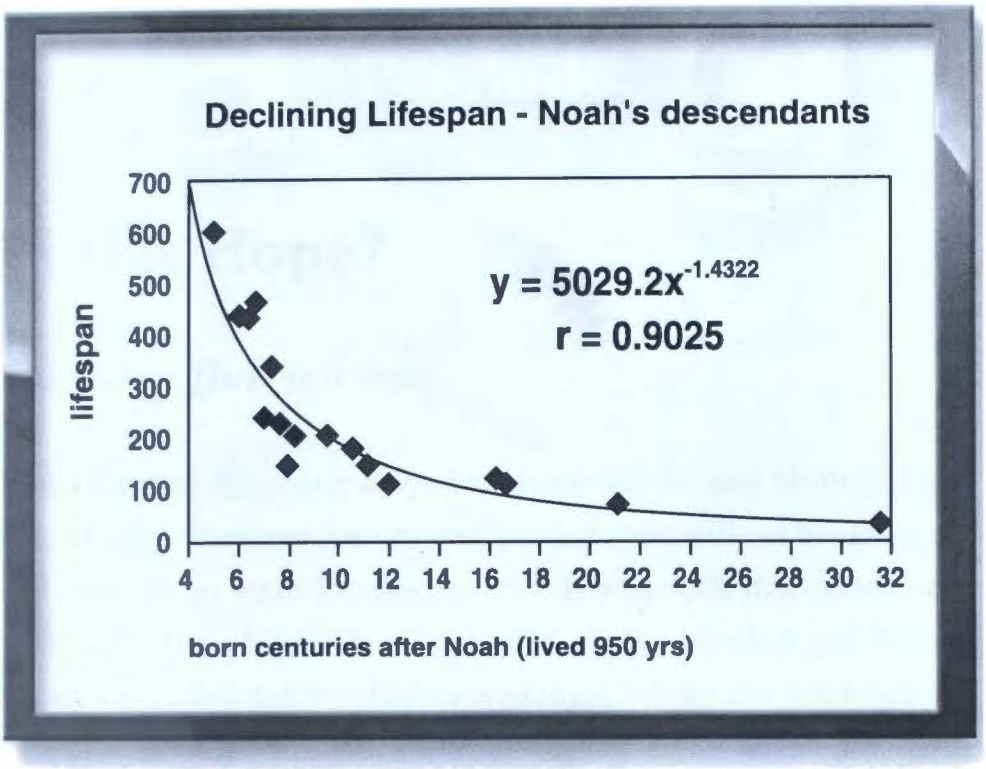
Information theory clearly indicates that information and information systems arise only through intelligent means and are only preserved by intelligence (Gitt, 1997). Computers and computer programs do not arise spontaneously. They are painstakingly designed. Even computer viruses, contrary to the public's perception, do not arise spontaneously. They are painstakingly and maliciously designed. The emergence of the Internet has created a vast experiment to see if information can

organize itself. It does not. Everything happening on the Internet, even the bad stuff, is designed.

It is the fundamental nature of information to degenerate. This reality is reflected all around us, from the illustration of the room full of whispers, to systems involving chains of command, to the routine crashing of our computer systems. The reason our information systems do not degenerate even *more* rapidly is because of elaborate, intelligently-designed systems created to stabilize and preserve that information. Yet even the best designed information systems, apart from intelligent maintenance and the *continual intervention* of intelligence, will always eventually breakdown. Computers are typically junk within 5 years.

The genetic systems of life can be seen as intelligently designed information systems, and natural selection can be seen as an intelligently designed stabilizing mechanism. Even though these systems appear to be superbly designed, they are still degenerating, apart from the intelligent intervention of their designer.

**What is the mystery of the genome? Its very existence is its mystery. Information and complexity which surpass human understanding are programmed into a space smaller than an invisible speck of dust. Mutation/selection cannot even begin to explain this. It should be very clear that our genome could not have arisen spontaneously. The only reasonable alternative to a spontaneous genome is a designed genome. Isn't that an awesome mystery–one worthy of our contemplation?**




## *Figure 14: Human life spans in early history.*

When Biblical life spans are plotted against time, for the generations after Noah, we see a dramatic decline in life expectancy with a strong appearance of a biological decay curve. Fitting the data to the "line of best fit" reveals an exponential curve following the formula $y = 5029.2x^{-1.43}$. The curve fits the data very well, with a correlation coefficient of 0.90. It seems highly unlikely this Biblical data could have been fabricated. The curve is very consistent with the concept of genomic degeneration caused by mutation accumulation. The curve is also very similar to the theoretical curves reflecting genomic degeneration shown in Figures 4 (p. 65) and 10b (p. 113).


# What Hope?

*Newsflash – There is a hope.*

As you have so diligently stayed with me all the way through this book, and have now reached its end, perhaps you will not be offended if I diverge from what has been a strictly scientific discussion and touch upon the philosophical. I would like to humbly put before you my own personal conclusion regarding where our hope lies.

When I was young, I accepted the fact that I was going to die, and that all of the people I loved were going to die. I accepted it, but it robbed me of joy, to say the least! I was taught that there was still one hope: that the world was getting better. Science was advancing. Culture was advancing. Even mankind was getting better. Through our efforts, we could make the world a better place. Through evolution, we could evolve into something better. Through *progress,* we might eventually defeat death itself. Perhaps we might someday even reverse the degeneration of the universe! My personal hope was that I might in some small way contribute to such progress. I believe that this basic hope was shared, to a large extent, by my entire generation*.

I now believe this was a false hope. I still believe we should diligently apply ourselves to making this a "better world", and to be responsible stewards of the world we have been given. But I see

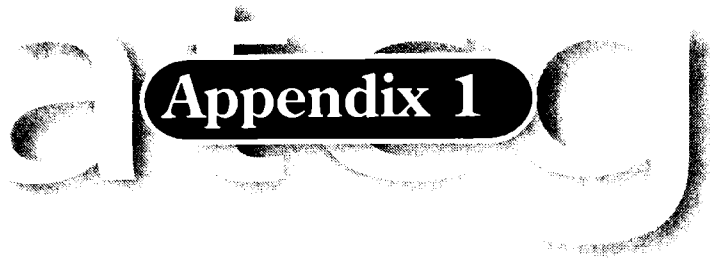
our efforts as a holding action at best. While science can reasonably hope to prolong life, it cannot defeat death. Degeneration is certain. Our bodies, our species, and our world are all dying. It is simply not in our power to stop this very fundamental process. Isn't this obvious when we look around us? So where is the hope? If the human genome is irreversibly degenerating, we must look beyond evolution in order to have a hope for the future.

One of my reviewers told me that the message of this book is both terrifying and depressing. He suggested that perhaps I am a little like a sadistic steward on board the Titanic, gleefully spreading the news that the ship is sinking. But that is not correct. I hate the consequences of entropy (degeneration). I hate to see it in my own body, in the failing health of loved ones, or in the deformity of a new-born baby. I find it all absolutely ghastly, but also absolutely undeniable. Surely a real steward on the Titanic would have a responsibility to let people know that the ship was sinking, even if some people might hate him for it. I feel I am in that position. Responsible people should be grateful to know the *bad news*, so they can constructively respond to it. If we have been putting all our hope in a sinking ship, would it not be expedient to recognize this and abandon the false hope? It is only in this light that we can appreciate bad news. Only in the light of the *bad news* can we really appreciate the *good news* that there is a lifeboat.

Even as we cannot create life, we cannot defeat death. Yet I assert there is One who *did* create life and who designed the genome. I do not know how He did it, but somehow He surely made the hardware, and He surely must have written the original software. He is called the Author of Life (Acts 3:15 – NIV). I believe the Author of Life has the power to defeat death and degeneration. I believe this is the ***good news***.

It is my personal belief that Jesus is our hope. I believe that apart from Him there is no hope. He gave us life in the first place, so He can give us new life today. He made heaven and earth in the first place, so He can make a *new* heaven and earth in the future. Because He rose from the dead, we can be raised from death, even the death which is already enveloping us. In these profound yet simple truths, I believe there is a true hope. I believe this hope is unshakable, because I believe it is founded on the One who is eternal. It is a hope that has withstood the attacks of time and the corruption of religion. It is a hope freely given to anyone who would receive it today. I humbly put before you this alternative paradigm for your consideration—Jesus is our one true hope.

* *Kimura, 1976: "Shall we be content to preserve ourselves as a superb example of living fossils on this tiny speck of the universe? Or, shall we try with all our might, to improve ourselves to become supermen, and to still higher forms, to expand into the wider part of the universe, and to show that life after all is not a meaningless episode?"*




# A Deeply Entrenched Ideology

*"It is obvious that the omnipotent power of natural selection can do all things, explain all things...."*

The above statement came from an early Darwinist, but I have lost the source. The ubiquitous nature of the philosophy underlying this statement makes its source irrelevant. It could have come from just about any Darwinist. In fact, just a few years ago I might have said it myself. More than 100 years after the above "statement of faith" was made, the Primary Axiom still captivates the minds and loyalties of most scientists. This is especially true among geneticists. However, when we look at numerous quotes from some of the most prominent population geneticists who ever lived, it appears that their commitment to the Primary Axiom is not based upon evidence, but is fundamentally an ideological commitment. Repeatedly, their own detailed analyses run counter to the Axiom. They seem to remain bound to the Axiom, not in light of their evidence, but in spite of their evidence. Hence they continuously need to explain why the Axiom can run counter to both common sense and their own data and yet still must be considered axiomatically true.

All the following quotes are from leading evolutionary geneticists (except for Hoyle, who was a prominent physicist). I hold these scientists to be highly competent, but I contend that they have built their work (perhaps their very lives?) upon a false axiom. I have extracted specific statements from their papers, which do not reflect their own philosophy, but which point to the problems I am raising.

Few university-based geneticists today would choose to openly discuss the weaknesses of the mutation/selection theory. Indeed, I suspect most geneticists have never even seriously considered such weaknesses

(although I am aware of numerous skeptics who choose to remain in the closet). Most university geneticists have never seriously questioned the Primary Axiom. This is because by faith they have always accepted it as axiomatically true, even as I once did myself. So they have not even bothered to examine the full extent of the problems with an open mind or an open heart. Every single study, every single paper, seems to be designed to make the theory work. The ideological commitment to the Primary Axiom among geneticists is tremendous. However, among some (I think the ones most secure in their faith in the Axiom) there has been open acknowledgement of specific problems. These acknowledged specific problems, when combined, powerfully argue against the Primary Axiom. The following quotes illustrate this (all emphases below are mine).

# Haldane's Dilemma

J.B.S. Haldane. 1957. The cost of natural selection. J. Genetics 55: 511-524.

"It is well known that breeders find difficulty in selecting simultaneously for all the qualities desired in a stock...***in this paper I shall try to make quantitative the fairly obvious statement that natural selection cannot occur with great intensity for a number of characters at once***..."

"I doubt if such high intensities of selection have been common in the course of evolution. I think n = 300 (300 generations), which would give I = 0.1 (10% total selective elimination in the population), is a more probable figure."

**"If two species differ at 1,000 loci, and the mean rate of gene substitution, as has been suggested, is one per 300 generations, it will take at least 300,000 generations (6 million years)..."**

***"Even the geological time scale is too short for such processes to go on in respect to thousands of loci...***can this slowness be avoided by selecting several genes at a time? I doubt it..."

"...the number of deaths needed to secure the substitution by natural selection of one gene...is about 30 times the number of organisms in a generation...***the mean time taken for each gene substitution is about 300 generations.***"

"...***I am convinced that quantitative arguments of the kind put forward here should play a part in all future discussions of evolution.***"

Haldane was the first to recognize there was a cost to selection which limited what it could realistically be expected to do. He did not fully realize that his thinking would create major problems for evolutionary theory. He calculated that, in man, it would take 6 million years to fix just 1,000 mutations (assuming 20 years per generation). He could not then know that the number of actual genetic units is 3 billion, and that

at least 1 million new mutations would be entering any hypothetical pre-human population each generation, most of which would require selection. Man and chimp differ by at least 150 million nucleotides, representing at least 40 million hypothetical mutations (Britten, 2002). If man evolved from a chimp-like creature, there were at least 20 million mutations fixed within the human lineage (40 million divided by 2), yet natural selection could only have selected for 1,000 of those. All the rest would have had to have been fixed by random drift, creating millions of nearly-neutral deleterious mutations. This would not just have made us inferior to our chimp-like ancestors, it would surely have killed us. Since Haldane's paper, there have been repeated efforts to sweep Haldane's dilemma under the rug, but the problem is still exactly the same. ReMine (1993, 2005) has extensively reviewed the problem, and has analyzed it using an entirely different mathematical formulation, obtaining identical results.

# Kimura's Quandary

Kimura, M. 1968. Evolutionary rate at the molecular level. Nature 217:624-626.

"...in the evolutionary history of mammals, nucleotide substitution has been so fast that, on average, one nucleotide pair has been substituted in the population roughly every two years. This figure is in sharp contrast to Haldane's well-known estimate...a new allele may be substituted in a population every 300 generations...." and "...at the rate of one substitution every two years...***the substitutional load becomes so large that no mammalian species could tolerate it***...." and "This brings us to the ***rather surprising conclusion...the mutation rate per generation for neutral mutations amounts to roughly...four per zygote***...."

Kimura's estimate of the actual mutation rate was 25-100 fold too low. But it is amazing how easily evolutionary theorists can accommodate any new data. They seem to have an infinitely flexible model, allowing continuous and unlimited development/revision of their many scenarios.

Kimura, M. The Neutral Theory of Molecular Evolution. Cambridge University Press. p.27.

"This formula shows that as ***compared to Haldane's formula the cost is larger by about 2***...under the assumption that the majority of mutation substitutions at the molecular level are carried out by positive selection***...to maintain the same population number and still carry out mutant substitutions...each parent must leave...3.27 million offspring to survive and reproduce***. This was the main argument I used when I presented the neutral mutation-random drift hypothesis of molecular evolution...."

Kimura realized that Haldane was correct, that selection must occur extremely slowly, and that it can only affect a limited number of mutations simultaneously. Kimura realized all the evolutionists of his time were evoking too much selection for too many loci, leading to absurd costs (for example, the need for more than 3 million offspring selected away for every adult!?). He developed his neutral theory in response to this overwhelming evolutionary problem. Paradoxically, his theory

led him to believe that most mutations are unselectable, and therefore most genetic information must be irrelevant, and most of evolution must be independent of selection! Because he was totally committed to the Primary Axiom, Kimura apparently never considered the possibility that his cost arguments could most rationally be used to argue against the Axiom's very validity.

# Muller's Fear

Muller, H.J. 1950. Our load of mutations. Amer. J. Human Genetics 2:111-176.

"It would mean an ever heaping up of mutant genes...degradation into utterly unrecognizable forms, differing chaotically from one individual of the population to another...it would in the end be far easier and more sensible to manufacture a complete man de novo, out of appropriately chosen raw materials, than to try to fashion into human form those pitiful relics which remained. For all of them would differ inordinately from one another, and each would present a whole series of most intricate research problems...if then the eliminated 20% failed involuntarily... the remaining 80%, although they had contrived to reproduce would on the whole differ from the doomed filth but slightly...practically all of them would have been sure failures under primitive conditions...***it is very difficult to estimate the rate of the degenerative genetic process***...." (pp. 146-7).

"...the open possibility that the deterioration consequent on the present relaxation of selection may after all be a good deal more rapid than has commonly been imagined...it is evident that the natural rate of mutation of man is so high, and his natural rate of reproduction so low, that not a great deal of margin is left for selection...if u has the minimal value of 0.1...an average reproductive rate of 2.4 children per individual would be necessary...without taking any account whatever of all the deaths and failures to reproduce for non-genetic causes***...it becomes perfectly evident that the present number of children per couple cannot be great enough to allow selection to keep pace with a mutation rate of 0.1...if, to make matters worse, u should be anything like as high as 0.5..., our present reproductive practices would be utterly out of line with human requirements.***" pp. 149-50.

Muller calculated that the human fertility rate of that time (1950) could not deal with a mutation rate of 0.1. Since that time, we have learned that the mutation rate is at least 1,000-fold higher than he thought. Furthermore, fertility rates have since declined sharply.

"...the present genetic load is a serious one...increasing it by only 25%... would be a matter of grave consequence, while its doubling would be calamitous...***if u should rise above 0.5, the amount of selective elimination required...would, as we have seen, be greater than the rate of effective reproduction of even primitive man would have allowed...genetic composition would deteriorate continuously, while the population would meanwhile diminish in numbers, all the way to the point of disappearance.***"

Muller concluded that if the mutation rate was as high as 0.5 early man could not have evolved. He would have degenerated and become extinct. But known mutation rates are 200-600 fold higher that this!

"...in many civilized nations, the birth rate is held down to an average of not much more than two per family, ***the upper mutation rate, that beyond which equilibrium is impossible, must be much lower than 0.5 and, as we have seen, perhaps lower than 0.1, even if selection were to be given full scope***." p. 155.

***"If we now postulated that the conditions of raised mutation rate, low birth rate...it would be very problematic whether or not this decline would eventually be arrested."*** p. 156.

If we established the most severe selection scheme, modern fertility levels would not be high enough to stop genetic deterioration if mutation rates are as high as 0.5. Since 1950, we have learned that our actual mutation rates are 100-300! Furthermore, fertility rates have sharply declined!

# Muller's Ratchet

Muller, H.J. 1964. The relation of recombination to mutational advance. Mutation Research 1:2-9.

***"There comes a level of advantage, however, that is too small to be effectively seized upon by selection, its voice being lost in the noise, so to speak.*** This level would necessarily differ greatly under different circumstances (genetic, ecological, etc.), but this is a subject which has as yet been subjected to little analysis...although deserving of it."

Muller anticipated the problem of near-neutral mutations, but failed to see the profound problems they create for evolutionary theory. He did realize that many diverse circumstances (not just population size) would amplify this problem.

"It might appear as though a species without recombination would be... subject to genetic degeneration...This might be thought to be the case... However, this conclusion, which was misleadingly stated by the present author in a recent abstract, is only valid for the artificial conceptualization... nevertheless...***an asexual population incorporates a kind of ratchet mechanism, such that...lines become more heavily loaded with mutation.***"

How extremely reticent Muller was to acknowledge the very problem which soon came to bear his name ("Muller's ratchet")! Throughout his career, Muller had a deep concern for radiation-induced mutation and human genetic degeneration and was a leading advocate of eugenics. However, even as he wanted to warn the public of the problem of genetic deterioration, he appeared to be extremely careful not to make any statements which might detract from the "certainty" of evolutionary theory (apparently this reflected where he placed his highest loyalty). His statements about the problem of genetic degeneration within asexual species (for which he became famous) are so cautiously worded that one can hardly discern his message.

Muller argued that his "ratchet" was of only limited relevance because he thought mutations were extremely rare. Therefore, he thought each mutation could be dealt with as a discrete and distinctly-selectable

unit and eliminated one at a time. We now know that mutations are numerous and diffuse, thwarting any possible "one-at-a-time" elimination mechanism.

If we combine Muller's recognition of near-neutral (i.e., unselectable) mutations with his recognition of mutational advance we see that no selection system can stop Muller's ratchet, even in sexual species. Even if selection could eliminate every mutation for numerous generations, eventually a new mutation would always sneak through. In asexual species, once a mutation is fixed in a genome there is no way to go back and get rid of it. Hence the information can only degenerate. It is a unidirectional (ratcheted) process. Each new generation will have to have more mutations than the last and so will be inferior to the last. Ironically, we should realize this is not just true in asexual species. It is also true in sexual species. The "ratchet" works because a certain fraction of the deleterious mutations will always sneak past selection and become fixed in the genome. These will still vastly outnumber any possible beneficial fixations. Selection cannot separate the few good from the many bad, because they are in large linkage blocks. They cannot be teased apart. Therefore, each part of the genome (each linkage block) must individually degenerate due to Muller's ratchet.

# Neel's Realization

J.V. Neel, et al. 1986. The rate with which spontaneous mutation alters the electrophoretic mobility of polypeptides. PNAS 83:389-393.

"...gamete rates for point mutations...on the order of 30 per generation... ***The implications of mutations of this magnitude for population genetics and evolutionary theory are profound.*** The first response of many population geneticists is to suggest that most of these occur in "silent" DNA and are of no real biological significance. Unfortunately for that line of reasoning...the amount of silent DNA is steadily shrinking. ***The question of how our species accommodates such mutation rates is central to evolutionary thought."***

# Kondrashov's Question

A.S. Kondrashov. 1995. Contamination of the genome by very slightly deleterious mutations: **Why have we not died 100 times over?** J. Theor. Biol. 175:583-594.

"Tachida (1990) concluded that VSDMs (very slight deleterious mutations) impairing only one function–its interaction with nucleosomes–may lead to too high a mutation load...."

"Lande (1994) and Lynch et al. (1994)...concluded...VSDMs can rapidly drive the population to extinction...."

"Simultaneous selection against many mutations can lead to further decline of $N_e$ and facilitate extinction (Li 1987; Lynch et al. 1984)."

***"I interpret the results in terms of the whole genome and show, in agreement with Tachida (1990), that VSDMs can cause too high a mutation load, even when $N_e = 10^6$-$10^7$***...conditions under which the load may be paradoxically high are quite realistic...."

"...the load can become excessive even when U<1...as my analysis suggests–contamination by VSDMs implies an excessive load, leading to stochastic mutation load paradox."

"...selection processes at different sites interfere with each other."

"...because the stochastic mutation load paradox appears real–it requires a resolution."

"Chetverikov (1926) assumed the mutational contamination of a species increases with time, leading perhaps to its eventual extinction."

***"accumulation of VSDMs in a lineage...acts like a time bomb... the existence of vertebrate lineages...should be limited to $10^6$-$10^7$ generations."***

If Dr. Kondrashov would believe his own data he would conclude that the Primary Axiom is wrong and that genomes must degenerate. Instead, he eventually appeals to "synergistic epistasis" to wave away the problems which he has so brilliantly characterized.

# Kondrashov's Numbers

S. Kondrashov. 2002. Direct estimates of human per nucleotide mutation rates at 20 loci causing Mendelian diseases. Human Mutation 21:12-27.

***"...the total number of new mutations per diploid human genome per generation is about 100...at least 10% of these are deleterious... analysis of human variability suggests that a normal person carries thousands of deleterious alleles...."***

Since this paper, Dr. Kondrashov has indicated to me by way of personal communication that 100 was just a lower estimate and that 300 is his upper estimate. He also indicated to me that he now believes up to 30% of the mutations may be deleterious. This means that, from his perspective, "U" (deleterious mutations per person per generation) would be 30-90. This is 100-fold higher than would have previously been considered possible. In the end, he dismisses the entire problem with "synergistic epistasis" and "truncation selection."

# Nachman and Crowell's Paradox

M.W. Nachman and S.L. Crowell. 2000. Estimate of the mutation rate per nucleotide in humans. Genetics 156: 297-304.

"The human diploid genome...about 175 new mutations per generation. ***The high deleterious mutation rate in humans presents a paradox. If mutations interact multiplicatively, the genetic load associated with such high U would be intolerable in species with a low rate of reproduction***...for U= 3, the average fitness is reduced to .05, or put differently, ***each female would need to produce 40 offspring for 2 to survive*** and maintain population size. This assumes that all mortality is due to selection...so ***the actual number of offspring required to maintain a constant population size is probably higher***."

According to Kondrashov, U (new deleterious mutations per person) is actually 10-30 fold higher than these authors claim (they are assuming 97% of the genome is silent junk). Furthermore, we know that, in reality, only a small fraction of total mortality can be attributed to selection. Despite their unrealistic assumptions, these authors still acknowledge a fundamental problem. However, they eventually wave it all away by evoking "synergistic epistasis."

# Walker/Keightley's Degeneration

A. Eyre-Walker and P. Keightley. 1999. High genomic deleterious mutation rates in Hominids. Nature 397:344-347.

"Under conservative assumptions, we estimate that an average of 4.2 amino-acid-altering mutations per diploid per generation have occurred in the human lineage...."

"...close to the upper limit tolerable by a species such as humans...a large number of slightly deleterious mutations may therefore have become fixed in hominid lineages... ***it is difficult to explain how human populations could have survived...a high rate of deleterious mutation (U >>1) is paradoxical in a species with a low reproductive rate...*** If a significant fraction of new mutations is mildly deleterious, these may accumulate...leading to gradual decline in fitness."

"***...deleterious mutations rate appears to be so high in humans and our close relatives that it is doubtful that such species could survive....***"

"...the level of constraint in hominid protein-coding sequences is very low, roughly half of all new non-synonymous mutations appear to have been accepted...if deleterious new mutations are accumulating at present, this could have damaging consequences for human health...."

These authors are still underestimating the extent of the mutation problem. They only consider the mutations within the protein-encoding portion of the genome. The functional genome is 10-30 fold larger than this. Even with these lower estimates, they acknowledge a fundamental problem and conclude that many deleterious mutations have accumulated during human evolution, and are probably still accumulating. Doesn't this clearly demonstrate that we are in fact degenerating and *not* evolving?

# Crow's Concerns

J.F. Crow. 1997. The high spontaneous mutation rate: is it a health risk? PNAS 94:8380-8386.

"...The overall impact of the mutation process must be deleterious... ***the typical mutation is very mild. It usually has no overt effect, but shows up as a small decease in viability or fertility...each mutation leads ultimately to one 'genetic death'***...would surely be an excessive load for the human population...so we have a problem."

"...there is a way out...by judicious choosing, several mutations may be picked off in the same victim...all individuals with more than a certain number of mutations are eliminated...***of course....natural selection does not line up individuals and remove all those with more than a certain number of mutations...the unreality of this model kept me for many years from considering this as a way which the population deals with a high mutation rate***...although truncation selection is totally unrealistic, quasi-truncation selection is reasonable."

***"It seems clear that for the past few centuries harmful mutations have been accumulating...The decrease in viability from mutation accumulation is some 1-2% per generation...***if war or famine force our descendants to a stone-age life they will have to be content with all the problems their stone-age ancestors had, plus mutations that have accumulated in the meantime...environmental improvements means that average survival and fertility are only slightly impaired by mutation...***I do regard mutation accumulation as a problem. It is something like the population bomb, but with a much longer fuse.***"

Dr. Crow acknowledges the fundamental evolutionary problems created by the discovery of high mutation rates, but tries to dismiss them using a very unrealistic theoretical model involving a very artificial selection system based on mutation count. Whether or not this artificial selection scheme employs truncation or "quasi-truncation" is just a matter of splitting hairs. He goes on to acknowledge that humanity must now be genetically inferior to our stone-age ancestors. This is an amazing confession about the reality of genomic degeneration.

Dr. Crow also comments on the inherently deleterious nature of mutations:

J.F. Crow. 1958. Genetic effects of radiation. Bulletin of the Atomic Scientists 14:19-20.

"Even if we didn't have a great deal of data on this point, we could still be quite sure on theoretical grounds that mutations would usually be detrimental. For a mutation is a random change of a highly organized, reasonably smoothly functioning living body. A random change in the highly integrated system of chemical processes which constitute life is almost certain to impair it–just as a random interchange of connections in a television set is not likely to improve the picture."

# Lynch et al.'s Mutation Meltdown

M. Lynch, J. Conery, and R. Burger. 1995. Mutation accumulation and the extinction of small populations. The American Naturalist 146:489-518.

"As deleterious mutations accumulate by fixation, there is a gradual decline in the mean viability of individuals...net reproductive rate is less...precipitates ***a synergistic interaction between random genetic drift and mutation accumulation, which we refer to as mutational meltdown...the length of the meltdown phase is generally quite short.***"

"These results suggest ***that for genetic reasons alone, sexual populations with effective population sizes smaller than 100 individuals are unlikely to persist for more than a few hundred generations***, especially if the fecundity is relatively low."

"...our results provide no evidence for the existence of a threshold population size beyond which a population is completely invulnerable to a mutational meltdown...."

"...simultaneously segregating mutations interfere with each others' elimination by natural selection...."

Lynch *et al.* understand that genetic degeneration is a major factor for all currently endangered species. They fail to go on to explain that the same would be true for most past extinctions, and that the basic process of extinction via genomic degeneration should logically apply to all higher genomes. They also acknowledge the problem of selection interference.

# Higgins and Lynch - More Meltdown

K. Higgins and M. Lynch. 2001. Metapopulation extinction caused by mutation accumulation. PNAS 98: 2928-2933.

"Here we show that metapopulation structure, habitat loss or fragmentation, and environmental stochasticity ***can be expected to greatly accelerate the accumulation of mildly deleterious mutations...to such a degree that even large metapopulations may be at risk of extinction***."

"...mildly deleterious mutations may create considerably larger mutational load...because individually they are nearly invisible to natural selection, although causing appreciable cumulative reduction in population viability."

"***We find that the accumulation of new mildly deleterious mutations fundamentally alters the scaling of extinction time...causing the extinction of populations that would be deemed safe on the basis of demography alone***."

"Under synchronous environmental fluctuations, the acceleration of extinction caused by mutation accumulation is striking... without mutation, extinction is 2,000 generations...***with mutation accumulation the extinction time is just slightly longer than 100 generations***...."

"For a metapopulation in unfragmented habitat, mildly deleterious mutations are more damaging than highly deleterious mutations... just as in the case with large carrying capacity, ***the mild mutational effects are the most damaging, causing minimal time to extinction***."

"Early work suggested...accumulation of deleterious mutations may threaten small isolated populations...here we show that accumulation of deleterious mutations may also be a significant threat to large metapopulations...***the decline is sudden, but extinction itself still takes a while to occur, the metapopulation may be completely inviable on intermediate or long time scales, although appearing***

***healthy on short time scales.***"

Higgins and Lynch make a strong case for genomic degeneration as a general problem for all mammals and all similar animal populations. They point out that currently existing genetic damage may ensure eventual extinction, even though it will take time to take effect. In the meantime, the species can still appear healthy and viable. Is that possible in the case of man? Human fertility and human sperm counts are both now dramatically declining (Carlsen et al., 1992). Many nations are now facing negative population growth, probably due to non-genetic causes. But is it not conceivable we could be in the early stages of mutational meltdown?

# Hoyle's Big Picture

F. Hoyle. 1999. Mathematics of Evolution. Acorn Enterprises, LLC, Memphis, TN. (note: unlike the others quoted here, Dr. Hoyle was not a geneticist, but a highly distinguished theoretical mathematician and physicist).

"The aging process shows, indeed, that ***statements one frequently hears, to the effect that the Darwinian theory is as obvious as the Earth going round the Sun, are either expressions of almost incredible naiveté or they are deceptions...with such widespread evidence of senescence in the world around us, it still seems amazing that so many people think it "obvious"*** that the biological system as a whole should be headed in the opposite direction...."

"The best natural selection can do, subject to a specific environment, is hold the deleterious mutations in check. ***When the environment is not fixed there is slow genetic erosion, however, which natural selection cannot prevent.***"

"...natural selection cannot turn back deleterious mutations if they are small, and over a long time a large number of small disadvantages escalate to a serious handicap. ***This long term inability of natural selection to preserve the integrity of genetic material sets a limit to its useful life....***"

# Howell's Challenge

Howell et al. 1996. Evolution of human mtDNA. How rapid does the human mitochondrial genome evolve? A. J. Hum. Genet. 59: 501-509.

***"We should increase our attention to the broader question of how (or whether) organisms can tolerate, in the sense of evolution, a genetic system with such a high mutational burden."***

Howell's challenge to us is based upon his own data, which suggested that the mutation rate just within the mitochondrial genome might be approaching one mutation per person per generation. He is right. Just 0.1-1.0 mitochondrial mutations per person create insurmountable problems for evolutionary theory. Yet this is nothing compared to the hundreds of mutations simultaneously occurring within the other chromosomes.

# Loewe's Limit

Loewe, L. 2006. Quantifying the genomic decay paradox due to Muller's ratchet in human mitochondrial DNA. Genet. Res., Camb 87:133-159.

***"A surprisingly large range of biologically realistic parameter combinations should have led to extinction of the evolutionary line leading to humans within 20 million years...."***

Loewe's limit for extinction is based upon only the damage associated with the mitochondrial genome, but the whole genome is 200,000 times larger!

# Appendix 2

# How Many Nucleotides Can Be Under Selection at One Time?

How many traits or nucleotides can be simultaneously selected for in a given breeding population? This is a very important question, and one that has not really been addressed adequately before. It is relevant to artificial breeding, population biology, and evolutionary theory. The question can be dealt with on a mathematical basis.

## Definition of C and c

Total selective cost (C) to a population is that fraction of the population that is *not* allowed to reproduce in order to achieve *all* selection. On the simplest level, we will assume that the fraction of the population which is selected against is C and that this fraction produces zero offspring. The remainder (1-C) is that part of the population which is selected for and is allowed to reproduce at the normal rate. Different species can afford different selective costs. For example, a plant species may produce one hundred seeds per plant. Such a species can afford to have a C value of 0.99. This means that 99% of the seedlings can be selected away and the population can still reproduce fully. In the case of man, the current human fertility rate is now roughly three children for every two adults. So in the human population only one child of the three can be selected away while still maintaining population size. In man, selective cost must be below 1/3 of the population and C must not exceed 0.33. In reality, even this cost is much too high. This is because there are many individuals who fail to reproduce for non-genetic reasons (accidental death, personal choice, etc.). We cannot know how often failure to reproduce is due to non-genetic effects, but it is surely very large. A realistic estimate of allowable selective cost in mankind must be less than 25%, probably near 10%. To be generous, we may assume C might be as high as 0.25. To determine upper theoretical limits for man, we may assume an unrealistically fertile

human population wherein C = 0.50 (half of all children are eliminated from the breeding population for genetic reasons every generation).

Cost per trait (c) is that part of the population eliminated due to the presence of a specific trait (or nucleotide). If we are selecting against a given trait (or nucleotide), we need to decide how strongly we will select against it. In other words, how much of the total population are we willing to eliminate to improve that trait? The part of the population that is eliminated for that trait is the selective cost (c) for that trait, and represents the "selection pressure" for that trait. For example, if 10% of the population is eliminated to affect a given trait, then for that trait c = 0.10. If c = 0.01, then 1% of a population is prevented from reproducing in order to affect that trait.

# Additive model

The simplest model to understand is the additive model. Here we assume that selection is additive and that selection for all traits is implemented simultaneously. For example, if we could afford to eliminate 25 individuals from a population of 100, we could simultaneously eliminate one individual to affect one trait and so we could affect 25 different traits (or 25 nucleotides). The general formulation would be as follows. Total population cost (C), would be the sum of all costs for each trait or nucleotide (c). So $C = c_1 + c_2 + c_3 \ldots c_n$, where "n" is the number of traits. Assuming that the selection pressure on each trait is the same, then C = n x c. In the case where selection pressure per trait is 0.001 (1 individual is eliminated out of 1000, to affect a given trait), and where total cost of selection is limited to 25% of the population, then 0.25 = n x 0.001. So in this instance, the maximal number of traits that can be selected for is 250. However, in such a case, even though 250 traits could be under selection, the selection pressure per trait would be vanishingly small, resulting in little or no selective progress over time. *Selective progress* approaches zero very rapidly, as more and more traits are put under selection (see Figure 6a, p. 84).

# Multiplicative model

The multiplicative model is more realistic and slightly more complex than the additive model. In this model there is first selection for one trait (or nucleotide) and then what is left of the population is subjected to selection for the next trait (or nucleotide). Selection is sequential rather than simultaneous. After one round of selection, the remainder of the population is mathematically 1-c. If there are two traits one wishes to select for, then one multiplies the remainder of each, (1-c) x (1-c), and then subtract from 1 to see the total cost of selection. For example if we eliminate 10% of a population for one trait and 10% of the remainder for a second trait our total cost is 1 - [(1-0.1) x (1-0.1)] = 0.19. In other words, 81% of the population remains to reproduce after selection for these two traits. For many (n) traits under selection, assuming that each trait undergoes approximately the same selection intensity, the equation can be generalized to $C = 1- (1-c)^n$.

In Figure 6b (p. 85), I have plotted the number of traits under selection against the maximal allowable selection intensity per trait, assuming a multiplicative model and C = 0.25 (25% of a human population can be eliminated for all selective purposes). As can be seen, the shape of this curve is essentially identical to the additive model. As the number of traits under selection increases, the allowable selection pressure per trait falls off exponentially, rapidly approaching zero. This basic pattern does not change even where the population is extremely fertile (Figure 6c, p. 86). If we could assume an exceedingly fertile human population (C = 0.5), allowable selection per trait falls off extremely rapidly as "n" increases. Even when considering an extremely fertile species, such as a seed-producing plant wherein C might be as high as 0.99, maximal allowable selection pressures become very small when there are more than 1000 traits (nucleotides) under selection.

What do these vanishingly small selection pressures mean? As the selection pressure for a trait approaches zero, selective progress also approaches zero, and the time to alter a trait via selection approaches infinity. As selective progress tends toward being infinitely small and infinitely slow, we realize we have a problem. This is because new mutations are constantly flooding into a population at high rates. We do not have "deep time" to remedy our degeneration problem. We need to

eliminate mutations as fast as they arise or mutations become embedded in the population due to drift and fixation. Even more significantly, as the allowable selection pressures get very small, at some point effective selection truly *stops*. This is because of the phenomenon of "noise" and genetic drift. *A point will always be reached where selection halts altogether*, depending on population size and the total amount of biological "noise" associated with reproduction.

The exact threshold where selection completely breaks down is somewhat fuzzy. However, some common sense can help put this issue in perspective. A selection system for a given trait that cannot even remove one individual from a breeding population of 1000 is certainly suspect! This corresponds to a selection cost for that trait of 0.001. Given the high level of noise within human populations, when the selection cost is less that 0.001, effective selection for that trait may cease entirely. Another way of saying this is as follows: in a population of 1000 people, if we are not allowed to remove even one (whole) person to affect a given trait, selection for that trait has effectively stopped and random drift is probably operational. Using the cutoff point of 0.001 and the additive model, we can calculate that we can maximally select for only 500 traits (nucleotides) in a realistic human population and only 990 traits in an idealized (extremely fertile) human population* (see Table 2). Yet what we know about human mutation rates indicates that we need to select for millions of nucleotide positions every generation in order to stop genomic degeneration!

** Kimura alludes to the same problem. Even though he does not show his calculations, he states that only 138 sites can be selected simultaneously when C=0.50, and s=0.01 (Kimura, 1983, p. 30).*

How many genic units can be selected simultaneously (assuming a minumum for c = .001)?

| C | $n^a$ | $n^m$ |
|---|---|---|
| .25 | 250 | 300 |
| .50 | 500 | 700 |
| .99 | 990 | 4,600 |

$n^a$ = The maximal number of genic traits that can be selected under an additive model.

$n^m$ = The maximal number of genic traits that can be selected under a multiplicative model.

***Table 2.***

How many nucleotides can be selected simultaneously?


# The Phenomenon of Unity and the Concept of Integrated Complexity

The puzzle of how to recognize Intelligent Design has been gradually coming together. There has always been an intuitive recognition of design in nature. This is the logical default perspective. To the extent that some people wish to reject the obvious, design was explicitly proclaimed through the scriptures (Genesis through Revelation). Later, design was argued by essentially all of the "Founding Fathers" of science, including Copernicus, Bacon, Newton, Pasteur, Maxwell, Faraday, and Kelvin. Paley (1802) was the first to put forward the argument of *complexity* as evidence of design. This concept has more recently been refined by Behe (1996) into the argument of *irreducible complexity*. The complexity argument has been further elaborated into the two related arguments, that of *information theory* (Gitt, 1997), and *specified complexity* (Demski, 1998). However, I believe there is still at least one more useful diagnostic of design, the phenomenon of Unity, which arises as a result of *integrated complexity*.

One diagnostic of design is the *comprehensive integration of a large numbers of components*, which is what I am calling **Integrated Complexity**. It underlies the easily recognizable natural phenomenon of **Unity**. Unity is an objective reality. Unity is readily recognized by any rational person, and is not merely subjective. Unity is therefore a legitimate subject of scientific analysis. Unity arises through the *comprehensive integration* of very many parts. A jigsaw puzzle has unity. A pile of sand does not.

A fighter jet is made up of thousands of component parts and countless atoms, but it has **Unity** of both function and form. This is what makes it readily recognizable as a product of design. It exists as a single integrated

unit, above and beyond all its components. In its original, undegenerated state, every single component has a purpose and a place, and each part is perfectly integrated with all the rest. Despite its countless components, the jet exists in a non-plural state. This is the essence of the term "unity" (oneness). We do not say, "Oh, look at all those pieces of metal and plastic." We say, "Oh, look at that plane." It is not even remotely adequate to say that a plane is more than the sum of its parts. A jet is a new reality existing on a totally different level than any of its parts. It can fly. The parts cannot. In a similar manner, it is foolish to say that a spaceship is more than lots of metal. It is also foolish to say that life is more than the sum of its parts. These are all obscene understatements. We might as well state that there is more than one drop of water in the sea. These things are so grossly obvious, how can we justify even saying them out loud unless we are talking to someone in a trance?

A human being contains over 100 trillion cells. But we **are not** 100 trillion cells. I repeat–that is not what we are. We are each truly a **singular entity**, united in form and function and being. We are the nearly perfect integration of countless components, and as such we comprise a singular new level of reality. The separateness of our existence as people–apart from our molecules–is both wonderfully profound and childishly obvious. Only a deep spiritual sleep could blind us to this reality. We desperately need to wake up. When we awake to the reality of unity, we also awake to the reality of *beauty*. We begin to realize that what we call "beauty" is simply the recognition of the comprehensive unity of designed things. In this light, beauty is not merely subjective. In this new light, beauty, like unity, can be seen as a truly objective and concrete reality*.

In their more poetic moments, scientists sometimes refer to the beauty of unity as *elegance*. Elegance is design that is so excellent and wonderful that every detail, every aspect, comes together perfectly to define something new–**a comprehensively integrated whole**. Unity can be

**As a personal aside, the converse of beauty is ugliness. I would suggest that ugliness is also an objective reality. Ugliness is the corruption of design, the marring of unity. This is why a wart can objectively be considered ugly. It is why aging is an uglifying process. It is why rusting cars, biological deformity, wars, and lies are all truly ugly.*

seen as the startling absence of loose ends or frayed edges. For example, in man, every cell has its place and function, in such a way as to specify **wholeness**. The human profile, like the profile of a sleek jet airplane, proclaims elegance of form and unity of purpose. I would like to submit to you that unity is the concrete and objective basis for what we call beauty. I believe it is also an unmistakable diagnostic for very high level design.

The amazing unity of a human body (our phenome) should be obvious to any thoughtful person who is even remotely acquainted with biology. When we see a human being, we do not think, "Look at all those cells and tissues." We see a single entity–a person.

What does this suggest about the human genome? The genome is the presumed basis underlying the phenome's unity. Yet amazingly, most modern geneticists see the genome as being essentially a disunited pile of nucleotides. All our collective genomes are said to merely comprise a "pool of genes". This is the very antithesis of unity. The genome is seen as a vast array of molecules, largely accidental and almost entirely random. Each nucleotide supposedly arose and is "evolving" (or drifting) independently. This entire pattern of thought (i.e., man is just a bag of molecules) is termed *reductionism*. The typical modern geneticist sees the genome as primarily "junk DNA", within which are imbedded over a million parasitic "selfish genes" (they also acknowledge that there are some real bits of information–a few tens-of-thousands of functional genes). It is widely assumed that each selfish gene has its own selfish agenda, propagating itself at the expense of the whole.

How could this be true? In light of the second law of thermodynamics, does it seem possible that the phenome's amazing unity and order arises entirely from a fragmented and chaotic genome? Rationally, if the order and unity of the phenome derives from the genome, then shouldn't the genome be *more complex* and *more integrated* than the phenome?

Imagine entering the intergalactic starship *S.S. Phenome*. You go past doors labeled "Warp Speed Engine Room" and "Holodeck". Then you see a door marked "Office of the Senior Architect and the Chief Engineer". You open the door and you see an office that is a complete wreck. Papers are strewn everywhere, there is the smell of rotting food, and computer screens are broken. Standing on a desk are two chimpanzees fighting

over a banana. Would you be so naive as to believe that you were actually looking at the Senior Architect and the Chief Engineer of the S.S. Phenome? Would you actually think the S.S. Phenome could have been *created* and *maintained* through this office in its degenerate and chaotic condition? Yet this is the modern view of the genome! This is the ruling paradigm regarding the genome's very nature, and describes the *idiotic master-genius slave* relationship of genome and phenome. In this light, shouldn't we be critically re-evaluating our view of the genome? Isn't it time for a paradigm shift?

If Integrated Complexity is actually diagnostic of design, and if the genome really was originally designed, we would predict the genome should show extensive evidence of integration and unity. We should be able to discover many levels of unity of form and function within the genome. I believe this is now beginning to happen. I predict that this will be seen more and more in the coming years, as we unravel the many elaborate and multi-dimensional patterns within the genome. I predict that when we understand the genome better, we will see integration and unity at all levels. But I also predict that we will see more and more evidence of degeneration and corruption of the original design, since mutation is degenerative and selection cannot prevent mutational degeneration. The genome is clearly experiencing an enormous amount of change due to our high rates of mutation. But it seems to me what we are seeing is entirely "downhill" change. Such random change cannot possibly be the origin of Integrated Complexity. Unity (comprehensively integrated complexity) simply cannot be built one mistake at a time (as the main body of this book clearly demonstrates).

The profound unity of life exposes reductionism for what it truly is: a type of spiritual blindness. Reductionism is simply a profound ignorance of the unity that is self-evident all around us. More specifically, the Primary Axiom, with its "gene pools" and independent evolution of individual nucleotides, is merely extreme reductionism applied to biology. It is thus inherently invalid. In a sense, this makes all the arguments of this book unnecessary. It is my personal conviction that even apart from the genetic arguments of this book the Primary Axiom is invalidated simply by the all-pervading reality of the phenomenon of Unity.


# Can Gene Duplication and Polyploidy Increase Genetic Information?

In opposition to the main thesis of this book, some would like to argue that duplication is the key to understanding how genetic information can increase spontaneously. It is certainly true that duplications occur spontaneously within all genetic systems. Duplication is a form of mutation, and the size of a duplication can be very small (one or just a few nucleotides) or very large (one chromosome or all chromosomes together are duplicated). When one chromosome is doubled it is called *aneuploidy*, when all chromosomes are doubled, this is called *polyploidy*. As with word-processing errors, a single letter can be duplicated, a single word can be duplicated, a whole chapter can be duplicated, a whole book can be duplicated, or the whole library can be duplicated. The question is this, "Do such duplications create new information?"

Iff I repeaaat a llettter, does it immmprove my sentenccce? If I repeat my sentence, do I tell you more? If I repeat my sentence, do I tell you more? If I repeat my sentence, do I tell you more? If this page occurred a second time elsewhere in this book, would the book be better? If every page of this book was written in duplicate, would you learn twice as much from it? Obviously, all these types of duplications are deleterious regardless of the scale. They do not increase communication and they obviously disrupt it. How could anyone think this type of duplication is a realistic method for the spontaneous amplification of useful information? The answer is, of course, that such people imagine combining mutational duplication with almighty selection. But we have just dedicated most of this book to showing that while selection can slow mutational loss of information, it cannot stop it. Most emphatically selection cannot reverse this loss. It should be obvious by now, if you have read this book, that nearly all duplications will be both deleterious and nearly-neutral, like all other

classes of mutation. This means selection will only be able to eliminate the very worst duplications. The rest will relentlessly accumulate and gradually destroy the genome.

Does biological observation support this common sense view of duplication? It most emphatically does! Let us consider the human population. Are there any polyploid humans? Of course not. Duplicating all the human genome is absolutely lethal. Are there any aneuploid humans? Yes there are–a significant number of people have one extra copy of one chromosome. Do these individuals have more information? Most emphatically they do not. While *aneuploidy* is entirely lethal for larger chromosomes, an extra copy of the smallest human chromosomes is not always lethal. Tragically, the individuals who have this type of "extra information" display severe genetic abnormalities. The most common example of this is Down's Syndrome, which results from an extra copy of chromosome 21. There are countless smaller duplications and insertions which also have been shown to cause genetic disease. It should be obvious by now that most duplications will be deleterious and nearly-neutral, like all other classes of mutation.

It is widely recognized that duplication, whether within a written text or within the living genome, destroys information. Rare exceptions may be found where a duplication is beneficial in some minor way (possibly resulting in some "fine tuning"), but this does not change the fact that random duplications overwhelmingly destroy information. In this respect, duplications are just like the other types of mutations.

After a given gene has been accumulating deleterious mutations for a long time, it is in a partially degenerated state. If that gene is then duplicated, the deleterious mutations are duplicated with it. Does such duplication in any way slow down the degeneration process? Obviously not! Upon careful consideration, we can see that once there is a duplicate copy of a gene, both copies will degenerate faster than before. Why is this? It is because each would then have a back-up copy and selection will become relaxed for both copies. It is often claimed that after a gene duplication one gene copy might then stay unchanged while the other might be free to evolve a new function. But neither of these events is actually feasible. Both copies will degenerate at approximately equal rates due to the accumulation of near-neutrals, as we have been learning. Neither can

stay unchanged. Furthermore, gene conversion should theoretically be continuously cross-contaminating both the reputed "un-changing copy" and the reputed "evolving copy". Gene conversions should theoretically also allow mutations within each gene to jump into the other copy, which should effectively increase the mutation rate for both copies. This will clearly also accelerate degeneration. In summary, duplicate genes should clearly contribute to mutual accelerated degeneration due to relaxed selection and accelerated mutation accumulation, and due to mutation scrambling via gene conversion. As if this is not enough, Chapter 9 clearly shows how unreasonable is the speculation that one gene copy is likely to evolve a new function while both copies are irrevocably degenerating.

What about polyploid plants? It has been claimed that since some plants are polyploid (having double the normal chromosome number), this proves that duplication must be beneficial and must increase information. Polyploidy was my special area of study for my PhD dissertation. Interestingly, it makes a great deal of difference how polyploidy arises. If somatic (body) cells are treated with the chemical called colchicine, cell division is disrupted, resulting in chromosome doubling but no new information. The plants that result are almost always stunted, morphologically distorted, and sterile. The reason for this should be obvious. The plants must waste twice as much energy to make twice as much DNA but with no new genetic information! The nucleus is roughly twice as large, disrupting proper cell shape and cell size. In fact, the plants actually have less information than before because a great deal of the information that controls gene regulation depends on gene copy number. Loss of regulatory control is loss of information. This is the same reason why an extra chromosome causes Down's Syndrome. Thousands of genes become improperly regulated because of the extra chromosome.

If somatic polyploidization is consistently deleterious, why are there any polyploid plants at all (e.g., potatoes)? The reason is that polyploidy can arise by a different process called "sexual polyploidization". This happens when an unreduced sperm unites with an unreduced egg. In this special case, all of the information within the two parents is combined into the offspring, and there can be a net gain in information within that single individual. But there is no more total information within the population. The information within the two parents was simply pooled. In such a case we are seeing pooling of information, but not any new information.

In a diploid organism, there can be two versions of the same gene. In such a heterozygous diploid, if one gene version is a dysfunctional mutant and the other is a functional non-mutant gene, the latter can act as a back-up copy of the former. Diploidy can thus be seen as a designed back-up system–designed in anticipation of the mutation problem. On the other hand, evolution cannot anticipate anything and so we can very reasonably conclude that it should never produce back-up systems. Sexual polyploidy essentially doubles potential heterozygosity, so there can be up to four versions of the same gene within the same individual. Such a system is thus doubly backed-up. Like the four redundant computers used on the space shuttle, there can be up to three mutant alleles at a given locus, but as long as the fourth is still functional, the plant is all right. So polyploidy does not provide a way to increase new information, but rather illustrates the importance of gene redundancy as a back-up system designed to effectively slow down degeneration. The cost of such back-up systems is that selection cannot remove mutations nearly as efficiently, so long-term degeneration is even more certain. In some special cases, the extra levels of genetic backup within a polyploid can outweigh the problems of disrupted gene regulation and reduced fertility, and so can result in a type of net gain. But such a "net gain" is more accurately described as a net reduction in the rate of degeneration.

What about duplicate genes and gene families? If having multiple gene versions can explain the utility of diploidy and polyploidy, it can likewise explain the utility of redundant copies of a given gene at different locations within the genome. Normally, when a redundant version of a gene is seen within another part of the genome, it is simply assumed by theorists that it must have arisen by an ancient gene duplication. They often add the general presumption of subsequent mutational divergence. But this is all based upon theoretical inferences, not observation. If a gene is redundant within the genome, such redundancy could just as logically be understood as having a designed function such as gene back-up or complex gene regulation.

The simple-minded notion that merely duplicating a gene might be beneficial is biologically naive. Yes, it is possible that a gene duplication might increase that gene's expression. In fact, this is sometimes seen. But simply increasing a gene's expression is usually deleterious (gene expression must be precisely regulated by elaborate and finely tuned

molecular systems). Furthermore, duplication is a remarkably inefficient way to achieve such increased gene expression. How could evolution be so consistently inefficient?

Lastly, actual gene duplications not only mess up their own expression, they routinely mess up the expression of other genes. Much of my own career was spent in the production of genetically engineered plants. Industry and academia spent over a billion dollars in this endeavor. What was quickly discovered was that multiple gene insertions consistently gave lower levels of expression than single gene insertions. Furthermore, the multiple insertions were consistently less stable in their expression (can you start to see that gene regulation is very complex?). Additionally, a large percentage of all transgenic plants displayed other genetic defects due to the disruptive effect of the extra DNA being randomly inserted into specific locations within the genome. Since the genome has a functional and highly specific architecture, any duplication or insertion should logically tend to disrupt that architecture. This is exactly what plant geneticists have been seeing.

The notion of gene duplication as a way to "evolve new information" has become very firmly entrenched within the evolutionary community. I believe this is partly because, "It must to be true! How else could evolution have happened?" I also believe that when a mantra is mouthed often enough, it takes on the appearance of unassailable truth. But careful analysis of what information really is, and how it arises, combined with a healthy dose of common sense, should reveal to us that random duplications are consistently bad. It is my personal opinion that "evolution through random duplications" is for the most part a widely-held *philosophical assumption*, rather than a scientifically-defensible observation. I believe that while it sounds quite sophisticated and respectable, it does not withstand honest and critical assessment.

*Author's note: The most crucial aspect of the genome is that it carries a massive amount of* ***functional information.*** *It is very unfortunate that functional genetic information has been confused with "Shannon information". The simplest way to clarify this confusion is to explain that Shannon information deals with potential information, while genomic information deals with genuine functional information. If you buy a Scrabble game, it comes with a set of letters. These letters represent a certain amount of potential information. If you make a message to a friend with these letters, they then represent functional information. If you buy a second Scrabble game, you have doubled your potential information. But you have not yet created any additional functional information (that requires intelligent ordering of the new letters). It is useful to note that functional information is what is communicated through language. Shannon information applies only to potential information (what set of letters do I have?), and always assumes a linear, one-dimensional informational code. Shannon developed his statistical methods for electronic communication systems (how many electronic bits might I send through a wire?), and he explicitly stated his concepts should not be applied to functional biological information systems.*


# Three Possible Objections

There are three possible objections to the thesis of this book which I would like to address in this appendix. These issues are not dealt with in the body of this book because they are for more advanced readers and would detract from the general readability of the main text.

## *Objection #1 – Mega-beneficial Mutations.*

If there were occasional rare mutations with a profoundly beneficial effect, such mutations might outweigh all the harmful effects of the accumulating deleterious mutations. This might halt degeneration. For example, perhaps a single nucleotide substitution might increase the information content of the genome by 1%. This would effectively counteract the mutation (or even the deletion) of 1% of the functional genome. In this hypothetical situation, that single point mutation could create as much information as might be contained in 30 million nucleotide sites. In this manner, a few mega-beneficial mutations could theoretically counteract millions of deleterious point mutations.

## *Objection overruled:*

The above scenario fails for four reasons:

a. The reductionist model of the genome is that the genome is basically a bag of genes and nucleotides, each gene or nucleotide acts largely in an additive manner. In such a model, essentially all information must be built up one tiny bit at a time, like building a pile of sand one grain at a time. This is even true in the special case of large DNA duplications. A duplicated region adds no new information until beneficial point mutations are somehow incorporated into it one nucleotide at a time. The reductionist theoretician may give some lip-service to the importance of interactions and synergy,

but, in reality, he knows that the only way to climb "Mount Improbable" is through a very long series of infinitesimally tiny steps. We can ask ourselves, rationally, "What type of improvements might we hope for via misspellings within a jet assembly manual?" Obviously any improvements, if they arose, would never involve large increments of improvement. At best they would involve very subtle refinements. At the heart of the Primary Axiom is slow incremental improvement. Under the Primary Axiom, we might safely say that a gene pool can only be filled up with information one tiny drop at a time.

b. In a genome with 3 billion units of information, the average beneficial mutation should only increase information by about one part in 3 billion. Yes, some beneficials will have more benefit than others, creating a natural distribution, but it is entirely unreasonable to believe that *any* beneficial point mutation could add as much information as, say, 30 million functional nucleotides.

Some might object to this point as follows: *"There are certainly lethal deleterious mutations. In these cases a single point mutation can effectively negate 3 billion units worth of information. In fairness, shouldn't the reciprocal be true for beneficials? Shouldn't the maximal beneficial mutation also be equal to 3 billion units of information?"* This line of thinking takes us back to the naïve, symmetrical-bell-shaped-curve view of mutation. But we know that that view is universally rejected. Why?

The extreme asymmetry of mutational effects has to do with the fact that one is trying to climb "Mount Improbable". Yes, it is conceivable that a mistake could cause you to stumble *up hill*, but only by a few feet. You will never stumble uphill by thousands of feet. However, a single error can easily cause you to fall *downward* very substantial distances. Indeed, while climbing Mount Improbable, you could easily plunge a very great distance–to an instant death. In the same way, if you are building a house of cards, failures are very easy, and are often very catastrophic, but you can only go *upward* one

card at a time. In a very similar way, mutational changes are profoundly asymmetrical.

c. The concept of using a few mega-beneficial mutations to replace the information being lost at millions of other nucleotide sites is not rational and leads to absurd conclusions. By this logic, just 100 mega-beneficial mutations, each of which might increase information by 1%, could replace the entire genome. One could delete all 3 billion bases within the genome and replace it with a genome consisting of just those 100 super-beneficial nucleotides. Indeed, if we could conceive of an information-doubling mutation (the mirror image of a lethal mutation), the entire rest of the genome could then be deleted. We would still have a fitness of 1.0, but based upon a genome of just one nucleotide! The mechanism of substituting a few mega-beneficials for millions of other information-bearing sites that are simultaneously being degraded by mutation would result in an effective genome size that was continuously and rapidly shrinking. This is obviously impossible. It would be like trying to improve a book by subtracting 1000 letters for every new letter added.

d. Oft-cited examples of apparent "mega-beneficial mutations" are very misleading. For illustration, let us consider antibiotic resistance in bacteria, fur coat thickness in dogs, and homeobox mutations in fruit fly.

Chromosomal mutations within bacteria that confer antibiotic resistance appear to be mega-beneficial mutations. In the presence of an antibiotic, the mutant strain lives, while all the other bacteria die. So fitness has not merely been doubled relative to the other bacteria, it has increased infinitely, going from zero to one!

If you take a Samoyed (arctic) dog and put it in the Sonora desert it will die. A mutation to "hairless" will allow adaptation to the extreme heat, so the dog will live. Fitness has again increased from zero to one, an infinitely large increase!

Certainly the two examples above are both "mega-beneficial mutations" in terms of adaptation to a specific environment.

But they are both loss-of-function mutations that reduce net information within the genome. In terms of information content, they are both still *deleterious* mutations. Almost all examples of what appear to be mega-beneficial mutations merely involve adaptation to a new environment. This is just a type of fine-tuning. It is not genome-building. The dramatic nature of these types of changes is not because the organism has "advanced" in any real way, but is only because everything else has died! It is only relative to the dead competitors that the mutant is seen as "improved". These types of mutations do not increase information, or create more specified complexity, or create in any way a higher form of life.

Very regrettably, evolutionists have treated two very different phenomenon, *adaptation to environments* and *evolution of higher life forms,* as if they were the same thing. We do not need to be geniuses to see that these are different issues. Adaptation can routinely be accomplished by loss of information or even developmental degeneration (loss of organs). However, development of higher life forms (representing more specified complexity) always requires a large increase in information.

There is a special class of mutations that can profoundly affect the development of an organism: mutations arising within what are called "homeobox" genes. These mutations can cause gross re-arrangements of organs. For example, a single mutation can convert an insect's antennae into a leg, or can cause a fly to have four wings instead of two. These mutations certainly qualify as mega-mutations. Such dramatic changes in body form, arising from simple mutations, have greatly excited many evolutionists. This class of mutation has created a whole new field of speculation termed "EvoDevo" (evolutionary development). This type of mutation is widely assumed to provide the Primary Axiom with macro-beneficial mutations, and might allow for evolutionary saltations (big jumps forward).

It is indeed conceivable that macro-alterations caused by homeobox mutations might sometimes be beneficial. It is even conceivable that they might sometimes be beneficial in a substantial way. But how often would this realistically happen, and could such point mutations really counteract genome-wide degeneration?

In terms of a jet manual, a single misspelling might convert the command "*repeat loop 3 times*" to "*repeat loop 33 times*". Or, a misspelling might convert the command "*attach assembly 21 into body part A*" into "*attach assembly 21 into body part Z*". These typographical errors could result in very profound changes in the shape of the airplane, but would they ever be beneficial? If they were beneficial, could they effectively offset the loss of information arising from millions of other misspellings that are acting to degrade all the other components of the plane?

We can theoretically acknowledge that homeobox mutations might occasionally be useful in some ways. However, the actual examples given are in fact profoundly deleterious. The antennae-leg in the fly is actually just a monstrosity. It neither acts as an antennae nor a leg. The fly with the extra set of wings cannot use them (they are not attached to muscles or nerves). Those useless appendages only interfere with the functioning of the normal pair of wings, and the mutant flies can barely fly. It should be obvious that some random changes within any instruction manual will produce gross aberrations within the finished product. But would this in any way support the idea that mega-beneficial mutations are happening? Would this suggest that one such macro-mutation could increase total genomic information by as much as 1% (30 million nucleotides in man)? Would it suggest that one such a mutation could counteract the degenerative effects of millions of mutations happening throughout the rest of the genome? Obviously not!

In conclusion, as much as they might help prop up the Primary Axiom, mega-beneficial mutations cannot be invoked.

## *Objection #2 – Noise can be averaged out.*

If a population is essentially infinite in size, and is perfectly homogeneous, and if "noise" is both constant and uniform, and if there is unlimited time, all noise effects will eventually be averaged out, and thus even near-neutrals might be subjected to selection. Under these conditions, it is conceivable that natural selection might eventually stop degeneration.

## *Objection overruled:*

None of these basic requirements for eliminating noise, as listed above, are ever met in nature:

a. Population size is never infinite, and in the case of man, population size has only become substantial in the last several thousands years. Evolutionists assume an effective evolutionary population size for mankind of only about 10,000. That small population would never have existed as a homogeneous gene pool, but would have only existed as isolated sub-populations, perhaps 100 tribes, each with about 100 individuals. Natural selection would have largely been limited to competition within each tribe. Under these conditions, there could be no significant noise averaging.

b. Noise is never uniform. In particular, environmental noise is highly inconsistent both spatially and temporally. For a tribe within a given region, the most important source of non-genetic noise might result from climatic extremes, but for a tribe in another region it might be disease. For many generations, nutritional variation may be the main source of noise confounding selection, followed by cycles of disease or warfare. Under these conditions, there will be no significant noise averaging.

c. As fitness declines due to mutation accumulation, the genomic background itself will be changing. In reference to selection for a given nucleotide, there will be progressively more and more noise from all the other segregating mutations which are accumulating. While some aspects of environmental noise will scale with fitness (thus diminishing proportionately as fitness declines), some aspects of environmental noise will

not scale with fitness, e.g., noise due to natural disasters. This latter type of noise, which does not diminish in concert with fitness decline, will grow progressively more disruptive to selection as fitness declines. Continuously increasing noise cannot be effectively neutralized by noise averaging.

d. When noise is high, selection becomes largely neutralized, resulting in rapid and catastrophic mutation accumulation. Given our low fertility and high mutation rate, there is little time for effective noise averaging to operate prior to our extinction. Noise averaging, to the extent it is happening at all, requires a huge number of selection events before there can be significant averaging. Since the hypothetical evolutionary human population would have been small, the only way to have huge numbers of selection events would be to average over many generations. However, long before noise averaging might help to effectively refine the selection process, the human population would go extinct (perhaps even before 1,000 generations). Fitness would reach zero long before mutational equilibrium could be reached. Noise averaging, even if it is actually happening, does not appear to be sufficient to halt the degeneration process soon enough to stop error catastrophe and extinction.

## *Objection #3 – The failure of the Primary Axiom is not a serious challenge to evolutionary thought.*

What does it matter if the Primary Axiom is fatally flawed and essentially falsified? The Primary Axiom is just one of numerous mechanisms of evolution, and so is not crucial to evolutionary theory. Evolutionary researchers just need some more time, and some more funding, to work out the few "minor kinks" in their various theories.

### *Objection overruled:*

This position is *damage control* and is clearly false:

a. **There is only <u>one</u> evolutionary mechanism**. That mechanism is mutation/selection (the Primary Axiom). There

is no viable alternative mechanism for the spontaneous generation of genomes. It is false to say that mutation/selection is only one of various mechanisms of evolution. There are several types of mutations and there are several types of selection, but there is still only one **basic evolutionary mechanism** (mutation/selection). The demise of the Primary Axiom leaves evolutionary theory without any viable mechanism. Without any naturalistic mechanism, evolution is not significantly different from any faith-based religion.

b. Darwin's only truly innovative concept was the idea that the *primary creative force* in nature might be natural selection. Yet he had no concept of genetics or mutation, and therefore had no conception of what was actually being "selected". So he was entirely ignorant of all the problems addressed in this book. His general view, that natural selection could explain all aspects of biology, was simply his vigorously advanced **philosophical** position. Not until much later did the neo-Darwinists synthesize genetics, mutation, and natural selection, creating the field of Population Genetics. Only then did Darwinism take on the appearance of real science. Ever since that time mutation/selection has been, and still remains, the singular lynch pin holding together all aspects of Darwinian thought.

c. Degeneration is the precise *antithesis* of evolutionary theory. Therefore the reality of Genetic Entropy is positively fatal to Darwinism. Many people are claiming that the concept of Intelligent Design cannot be approached scientifically and is only a matter of faith. However, it is obvious that in biology the "Null Hypothesis" of Intelligent Design is mutation/selection. We all know that to disprove a Null Hypothesis is to strongly support The Hypothesis. Therefore, any scientific evidence demonstrating that mutation/selection **cannot** create or preserve genomes is sound scientific evidence **supporting** Intelligent Design.

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# Glossary

***Adaptation*** – Organisms interact with their external environment, and mutations can affect this interaction. Such mutations can affect adaptation to an environment, making the interaction better or worse. Adaptive mutations provide the best examples of beneficial mutations, and selection for such mutations is the basis for what is called "micro-evolution". However most of the information within a genome is not relevant to environmental adaptation, but controls the wonderfully complex inner-workings of a living system.

***Chromosome*** – Most genomes are divided into sub-units called chromosomes. These are like volumes within an encyclopedia. Each human chromosome has millions of nucleotides and thousands of genes.

***Cost of selection*** – The cost of selection is the failure of individuals to reproduce. In order to have selection operate, some individuals must under-reproduce. This cost can be temporarily suspended as long as a population is continuously growing (everyone could reproduce, but some more than others), but in deep time, population growth must be merely episodic by necessity.

***Entropy*** – In its most general or common usage, entropy is the universal tendency for things to degenerate apart from intelligent intervention. Entropy is sometimes defined as "the natural tendency for thing to go from order to disorder". It is also described as "the tendency for energy to go from useful forms to useless forms". It is also described as the "inability for machines to operate at 100% efficiency". It is also called "time's arrow" or "the vector of

the universe", because entropy always increases in the big picture. Einstein considered it the most important force in the universe, and we personally experience it every day of our lives.

***Epistasis*** – The different mutations that affect the same trait often interact, and when this happens, it is called epistasis. A deleterious mutation may be much more or less deleterious depending on the absence or presence of other mutations. Such epistasis creates non-heritable noise and strongly interferes with selection. Geneticists acknowledge that epistasis is important, but assume that positive and negative interactions largely cancel each other out.

***Error catastrophe*** – The biological situation where deleterious mutations are accumulating faster than selection can remove them, leading to a continuous net decline in fitness every generation. Unless reversed, error catastrophe leads to the extinction of a population.

***Functional information*** – When we use the word information in the normal sense of the word, we are speaking of functional information. Functional information communicates something, and for a specific purpose. Data compression allows us to communicate more functional information using fewer numbers or characters.

***Gene*** – A biologically functional unit within a chromosome. Genes are made up of thousands or even millions of nucleotides. These are analogous to chapters in a book. A typical human gene is poly-functional, coding for many different RNAs and various protein forms. Genes are regulated by very complex machinery, including DNA sequences far beyond the gene's borders.

***Gene pool*** – The abstract concept of a gene pool has no correspondence to reality. Genes (alleles, nucleotides), never exist in freely mixing pools, but only exist in living organisms, in the context of specific linkage blocks within chromosomes. The concept of a gene pool is sometimes useful when we need a mental picture of different alleles increasing or decreasing independently within a population.

***Genetic drift*** – Because each new generation arises by a sampling of gametes produced from the previous generation, random sampling error will cause all alleles to slowly increase or decrease in frequency. Such genetic drift is the unavoidable result of Mendelian segregation and random gametic sampling. Drift is especially strong in small populations, and tends to negate almost all selection. Selection is essentially neutralized in very small populations (except selection against near-lethal mutations), and alleles are quickly lost or fixed randomly regardless of their fitness effect.

***Genetic entropy*** – This is a fundamental biological principle. Apart from intelligent intervention, the functional genomic information within free-living organisms (excluding viruses) must consistently decrease. Like all other aspects of the world we live in, the "natural vector" within the biological realm is degeneration, with disorder consistently increasing over time.

***Genetic linkage*** – A chromosome is a linear molecule somewhat like a very long text message. Corresponding chromosome pairs can swap blocks of information, like two text messages might swap their final paragraphs. This type of informational swapping is limited to large blocks of DNA. Whole paragraphs are exchanged. Individual words or letters are not normally swapped. Within a linkage block (paragraph), all letters and words are physically linked together and are never separated. The typical human linkage in block is about 20,000 nucleotides. They are essentially indivisible and are thus inherited as a single unit.

***Genetic load*** – The genetic load of a population consists of all deleterious mutations presently within that population. When genetic load is increasing continuously, a population is in error catastrophe.

***Genome*** – The entire genetic content of an organism. This includes all DNA, all genes, and all chromosomes. The functional genome is the entire physical genome, minus any portions that are biologically irrelevant (having no functional information and zero biological effect).

***Genotype*** – A genotype is a personal version of the genome. It is a specific array of genetic alleles, present in a specific individual within a specific population.

***Genotype value*** – The genotype value can be seen as the total information content of an individual's genome. It is that part of an individual's total biological functionality that is specified by the individual's genome. Genotype value is different from phenotype value because of environmental factors (phenotypic noise), which also affects an individual's biological functionality. The extent that a given mutation changes genotypic value is a function of its specific mutation fitness effect. Genotype value can be used as being synonymous with the term "genotype fitness".

***Haldane's dilemma*** – The famous geneticist Haldane analyzed the cost of selection and found that, even given a steady supply of selectable beneficial mutations, the rate that such mutations can be selectively fixed is extremely slow (300 generations per fixed mutation). This means that forward evolution becomes impractical even within geological time frames. This problem has been confirmed by others.

***Heritability*** – A traditional measure of the signal-to-noise ratio as it applies to selection. Specifically, it is the heritable variance divided by total variance. Total variance combines heritable variation (signal) and non-heritable variation (noise). Non-heritable noise includes all variance due to environmental affects, environment-by-genotype effects, epistatic effects, and dominance effects.

***Integrated complexity*** – Perfectly integrated complexity results in Unity. Perfect integration arises when every piece of a puzzle is fitted to every other piece, with no missing parts and with no loose ends. Neither "co-option" nor "pre-adaptation" can explain this type of perfection (both mechanisms produce "jerry-built" contrivances). Natural selection lacks the almost infinite resolution needed to explain this type of perfection. A garbage pile in complex, but it is not integrated. However, assembled jigsaw puzzles and working jet planes manifest Integrated Complexity.

***Kimura's box*** – Muller realized that mutations that had very small fitness effects would be unselectable. Kimura formalized this principle mathematically and described a threshold where mutational effects would become "effectively neutral" (i.e., unselectable). Kimura argued that most mutations would fall into this class and that the principle of "effectively neutral" applies equally well to both beneficial and deleterious mutations. In plotting mutational fitness effects, one can envision a zone (or "box") surrounding truly neutral mutations (those with absolutely zero effect). The more non-heritable noise that exists within a genetic system, the larger the "no-selection" box. Kimura pointed out that population size helps define the size of this no-selection zone (small populations have more noise due to gametic sampling). However, the size of this no-selection zone is also affected by many other types of noise, including environmental and reproductive noise. In large genomes, the majority of mutations must fall within Kimura's no-selection box.

***Mendel's Accountant (MENDEL)*** – An advanced computer simulation program that realistically models how genomes change over time in response to mutation/selection.

***Muller's ratchet*** – The only way to get rid of deleterious mutations is to maintain entire chromosomes which are "uncontaminated" by mutations. Since every chromosome is receiving many new mutations, the only realistic hope for achieving this is to systematically splice together the uncontaminated portions of matching chromosomes. This might appear conceivable because splicing (recombination) really does occur, and selection might strongly favor "purified" recombinant chromosomes. However, Muller showed that this cannot realistically happen because recombination is very imperfect; it does not occur within genetic linkage blocks, but only between them. Since slightly deleterious mutations accumulate within all linkage blocks, there is no mechanism to purify the chromosomes. Swapping one linkage block for another merely replaces one set of mutations for another. Even if a very beneficial mutation occurs within a given linkage block, it is irrevocably linked to all the deleterious mutations already in that block, and so its benefit is thereby negated. Therefore, genomic

change has a "ratchet mechanism" such that genetic damage is not reversible.

***Mutant allele*** – All the derived copies of an initial mutation being passed down from generation to generation. A given mutant allele can increase or decrease in frequency within a population. If a mutant allele reaches a frequency of 1.0, it has reached fixation (All individuals in the population have two copies of the mutation. No non-mutant alleles are left).

***Mutant allele frequency*** – The fraction of all alleles at a particular locus (for diploids this is double the population size) that are the mutant form. If there are 2 copies of a mutation in a diploid population of 100, the mutant allele frequency is 1% and the non-mutant allele frequency is 99%.

***Mutant locus*** – The location of a mutation, in terms of its position within a linkage block, within a chromosome.

***Mutation*** – Any change in the genome that was not present previously. Mutational changes are directly analogous to word processing errors which arise in the copying of a text. There can be substitutions, deletions, insertions, duplications, inversions, etc.

***Mutational meltdown*** – The final phase of error catastrophe. As a population's fitness continually declines, the population's fertility eventually begins to decline. When there are fewer offspring per female there is less surplus population available for the selective removal of accumulating deleterious mutations. This leads to accelerating fitness decline, which leads to accelerating fertility decline, and hence less and less selection. This final phase of degeneration leads to a rapid collapse of the population and sudden extinction.

***Mutation fitness effect*** – The biological effect of a mutation. Mutation fitness effects can be positive or negative, large or small. The mutation effect is expressed as the relative change in an individual's total biological functionality, caused by a change in an individual's genotype value. A deleterious mutation with a

fitness effect of -0.01 decreases an individual's genotype value by one percent. One percent of the genomic information is lost. Total biological functionality is reduced by 1%. Another way of saying this is that such a mutation decreases genotypic fitness by 1%. These are all just alternative ways of describing the biological effect of a mutation. Mutation effect is independent of environmental variation (phenotypic noise), and random aspects of reproduction (reproductive noise). Mutation effect is similar but not identical to the traditional concept of a selection coefficient (see Sanford et al., 2007a).

***Mutation/selection chain*** – In the real biological world, this is the chain of events that links a mutational event to a selection event. A mutation affects a linkage block, which affects a chromosome, which affects a genotype, which affects a phenotype, which affects the reproductive fitness of an individual, which affects the actual transmission of the mutation into the next generation. There is biological noise at each link in this chain, and so each link of this chain is associated with an imperfect correlation.

***Natural selection*** – Natural selection is the natural tendency for less biologically functional individuals within a population to reproduce less than those who are more functional. When the more function individuals reproduce, it is often called "survival of the fittest", but it would be better called "reproduction of the fittest". In nature there is also a great deal of randomness to reproduction. This important principle can be termed "survival (reproduction) of the luckiest". Because both principles are operational in nature, the most fit individuals only have a slightly higher probability of reproduction and they may be excluded from reproduction due to random events. This natural type of selection is also called "probability selection". It is a very ineffective form of selection (see truncation selection).

***Nucleotides*** – Nucleotides are the four different molecules that constitute the "rungs" in the DNA ladder. They are typically represented as A, T, C, and G. Many nucleotides are poly-functional, affecting various biological processes simultaneously.

***Phenome*** – An entire functional organism, combining all aspects of its genotype and phenotype. The outward expression of all the information of a genome within a specific environment.

***Phenotype*** – The actual manifested biologically functional individual. The phenotype is affected by both the genotype and the environmental factors surrounding the individual. Genotype and phenotype are correlated, but they are not identical.

***Phenotype value*** – The actual biological functionality of an individual relative to other individuals in the population, as determined by the combination of genotypic effects and environmental effects, is called "phenotype value". It is what selection actually acts upon. It is what Mother Nature actually sees. Phenotype value is synonymous with the terms "phenotypic fitness" or "biological fitness", as reflected by the common use of these terms among biologists. However the concept of phenotype value (phenotypic fitness) is distinct from what population geneticists would formally define as "fitness". For clarity, we will use the term reproductive fitness to refer to the traditional population geneticist's definition of fitness, which is distinct from phenotypic fitness.

***Poly-functional DNA*** – It is increasingly clear that there are multiple, overlapping, functional patterns within higher genomes. This means that many nucleotides do not have one function but actually have several functions (even as a letter in a word puzzle can be part of two words). Poly-functional DNA is interesting because it is poly-constrained and is severely limited in terms having any potential beneficial mutations.

***Population*** – An inter-breeding group of individual is a population. The population size is the number of reproducing individuals.

***Primary Axiom*** – The foundational belief underlying all Darwinian thought is that that **mutation plus natural selection** can explain all aspects of life. Another term for this is neo-Darwinian theory.

***Reproductive fitness*** – I define this term as the product of "phenotypic value" (phenotypic fitness) and "reproductive noise". Reproductive noise arises because actual success in reproduction is not just determined by biological functionality, but also by random reproductive factors. So phenotypic fitness and reproductive fitness are correlated, but not identical. The strength of correlation between phenotype value and reproductive fitness depends upon the selection scheme employed. Artificial truncation will yield the highest possible correlation, while classical probability selection will yield the lowest correlation. What I am calling "reproductive fitness" is sometimes called "Darwinian fitness" or "Wrightian fitness", after Sewell Wright, the first to mathematically formulate "Darwinian fitness".

***Selection*** – Selection can be viewed as differential reproduction, where some individuals reproduce less than others. Some individuals are differentially excluded from contributing to the next generation. Unless there is a surplus population (i.e., excess fertility), selection cannot happen without the population size shrinking due to the non-reproduction of individuals.

***Selection Interference*** – The phenomenon where selection for one trait in a population confounds the selection for another trait in the same population.

***Shannon entropy*** – A statistical measure of complexity ("non-simplicity"). This statistic helps define the lower limits of potential information. An alphabetic sequence of letters (a, b, c...) has low Shannon entropy, because the sequence is fixed and predictable. This limits the amount of information it carries. So low Shannon entropy means limited information potential. The same set of letters can be made "complex" by re-ordering them. Arranging them into a useful message that communicates something increases Shannon entropy, but so does just scrambling the letters. In the first case, true functional information is created (through intelligence). In the second case, there is still only potential information (a randomized set of letters). Therefore, increasing Shannon entropy should not be confused with increasing functional information. True information has high Shannon entropy, but so does informational junk.

***Shannon information*** – A statistical measure of potential information. More letters and more types of letters both increase potential information. However, unless letters are placed in a specified and meaningful sequence, there will always be zero functional information, and nothing can be communicated. By scrambling the letters of a coherent message, we maintain the same amount of potential information, but eliminate all functional (actual) information.

***Synergistic epistasis*** – The term synergistic epistasis is normally only used in attempting to rationalize how genomes might be prevented from degenerating continuously. The basic concept is that epistasis (interaction) between mutations is consistently negative. Therefore, as mutations accumulate, each new mutation has a greater and greater average fitness deleterious effect. This is the exact opposite of the standard multiplicative population genetics model, wherein each mutation has less and less effect (one or both models must be wrong). The synergistic epistasis model is extremely artificial and biologically un-realistic. Even if the model is granted, it can be shown that this mechanism fails to stop degeneration when linkage and the interaction between mutations and non-mutations are also taken into account.

***Truncation selection*** – When plant or animal breeders use artificial selection they typically use truncation selection. The best individuals are selected with certainty and the worst are excluded with certainty. This form of selection is not normally operational in nature. In special cases, where there is almost certain death for all but a few well-defined genotypes (i.e., antibiotic resistance in bacteria), episodes of truncation selection can happen in nature. This is a very strong form of selection, but natural populations could only survive rare episodes of such stringent selection because it is associated with extremely high rates of mortality.

# Index

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# Genetic Entropy and Mendel's Accountant

The simple logic described in this book strongly refutes neo-Darwinian theory. However, the Primary Axiom is now so deeply entrenched in people's minds that some will require evidence beyond a straight-forward logical analysis. But apart from logic, can we objectively and empirically test neo-Darwinian theory to the satisfaction of reasonable people?

There is only one empirical and definitive method to objectively analyze neo-Darwinian theory. That method is called "numerical simulation". In real populations, millions of mutations are segregating simultaneously. This makes the mutation/selection process amazingly complex. Because of this complexity, the only way to understand the process is to systematically track every mutation that occurs within a population (in the same way an accountant uses a spreadsheet to track multiple financial transactions). This is

the essence of what is called "numerical simulation". When applied to genetic systems, numerical simulation can be termed "genetic accounting".

The program *Mendel's Accountant* was developed for this purpose. It is the first biologically-realistic, forward-time numerical simulation program for population genetics. This new program is a powerful research and teaching tool. When any reasonable set of biological parameters are used, *Mendel's Accountant* provides overwhelming empirical evidence that genomes degenerate over time and that all of the flaws inherent in evolutionary genetic theory are real. This effectively falsifies the Primary Axiom with a degree of certainty that should satisfy any open-minded person.

Mendel's Accountant is a program that can be run using a PC. It can be downloaded along with a detailed description and set of instructions free of charge at http://mendelsaccountant.info.

The scientific implications of Mendel's Accountant are summarized in the upcoming book *Genetic Entropy and Mendel's Accountant.*